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## Original Articles

# THE TWENTY-NINTH MAUDSLEY LECTURE: THE ROLE OF THE TEMPORAL CORTEX IN CERTAIN PSYCHICAL PHENOMENA

By

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THE Founder of this lecture series was described with consummate skill by Professor Aubrey Lewis in the Twenty-fifth Maudsley Lecture, before this Association. Henry Maudsley was a clinician who turned again and again to the problem I shall approach today. He even wrote a monograph under the daring title of "The Physiology and Pathology of the Mind".

Always a severe critic of current opinion and dissatisfied with the contemporary care of psychiatric patients, Maudsley pledged his personal fortune to bring about a better order of things. The Maudsley Hospital is the realization of his dream. The splendid service that it gives to patients today and the great distinction of its staff bear eloquent witness to the wisdom of Maudsley's plan.

Psychical responses to electrical stimulation present many new problems of physiology. It was in 1934 that a patient, who was being operated upon under local anaesthesia, first told me that she seemed to be re-living a previous experience as the result of, or rather during, temporal lobe stimulation. She said she saw herself as she had been while giving birth to her baby. I recorded the event and waited.

Since that time there have been many other examples of psychical phenomena produced by electrical stimulation and I have realized that here was material of considerable interest to psychiatrists. But I postponed presenting the material to them, realizing that, although the facts were obvious, their meaning in terms of physiology was obscure. And so I have waited year after year for the accumulation of more evidence.

It was the invitation to give the Maudsley Lecture that finally impelled me to take the plunge. Time will tell whether I have produced useful hypotheses to explain the facts.

## A. THE STREAM OF CONSCIOUSNESS

The first stage of this study was presented to the International Congress of Psychology last June.* At this time I reported some of the evidence that has to do with the permanent ganglionic record of life's experience. Long ago William James (1910) described the "stream of thought", or the "stream of consciousness", as a river forever flowing, forever changing, different in content in each succeeding unit of time.

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* Address to the Fourteenth Meeting of the International Congress of Psychology, 9 June, 1954, Montreal. This will appear shortly in *Acta Psychologica*.

The record of the stream of consciousness can be reactivated occasionally by electrical stimulation of the cortex of the temporal lobe, or by epileptic discharge restricted to the same area. When stimulation of the exposed cortex produces such a result in a conscious patient, it seems to him that he is re-living an earlier period of time in the greatest detail. Although he retains awareness of his actual surroundings, there is a re-experiencing of visual, auditory, and even somatic sensations; action goes forward and the interpretation and the understanding that belonged with that moment of time are reproduced.

This is a psychical response that may be described as *experiential.* There are other psychical responses also. We may call them *interpretive* since they consist in alterations of the interpretation of current experience.

Perhaps an objective description of experiential and interpretive responses may be of interest to psychiatrists as well as psychologists.

Psychical responses to stimulation are very different from the gross movements that may be produced by electrical stimulation of the motor cortex of mammal and man, very different from the elementary sensory responses reported by man when one of the various sensory areas of the cortex is stimulated. They constitute a new order of physiological phenomena, but one which Hughlings Jackson recognized years ago as occurring spontaneously in epileptic patients. He called them "dreamy states".

## B. THE GANGLIONIC RECORD

The record of the stream of consciousness may be activated as though it were a strip of cinematographic film recording the sight and sound, the movement and meaning which belonged to each successive period of time. When a stimulating electrode sets off an experiential response, action may go forward as long as the stimulation continues.

Strange as it may seem there is no confusion of different experiences. During the time that the electrode is applied to the temporal cortex, delivering for example 60 impulses per second, one portion of the stream of consciousness, and one only, is caused to flow again through a man's mind, as though there were, in addition to the activation, an inhibitory effect on the other portions of the recording mechanism.

Since the electrode may activate thus a random sample of this strip from the distant past, and since the most unimportant and completely forgotten periods of time may appear in this sampling, it seems reasonable to suppose that the ganglionic record is complete and that it really does include all periods of each individual's waking, conscious life.

How is this record preserved, and how is it formed in the first place? One might surmise that there is a constant succession of impulses projected from the zone of central integration outward to the temporal regions, forming, among the millions of ganglion cells that cover the temporal lobes like a vast carpet,* a continuous pathway. The pathway must undergo a physical change so that a simple electrical current can follow it years later. Thus, present experience would be preserved for a life-time, preserved by means of successive facilitation through the cells and synapses which thus constitute the pathway.

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* It may be that the pathway of facilitation is actually located in grey matter of some other area with which the temporal cortex is intimately connected, such as the hippocampal zone.

Let us consider this hypothesis from another point of view. When present experience slips into past experience the ganglionic record becomes part of a continuous trail of facilitation that runs backward through 20 years of waking life and more! But it is a trail that can never be followed backward. It runs, like a one-way street, forward from any point at which stimulation makes an entrance into it.

As to the localization and the organization of the ganglionic mechanism of this record we have no certain information except the fact that it can be activated by an electrode on the temporal cortex, not elsewhere. As far as our experience goes it can only be activated in a temporal cortex that has been somehow conditioned by years of electrical discharges from a neighbouring epileptogenic focus.

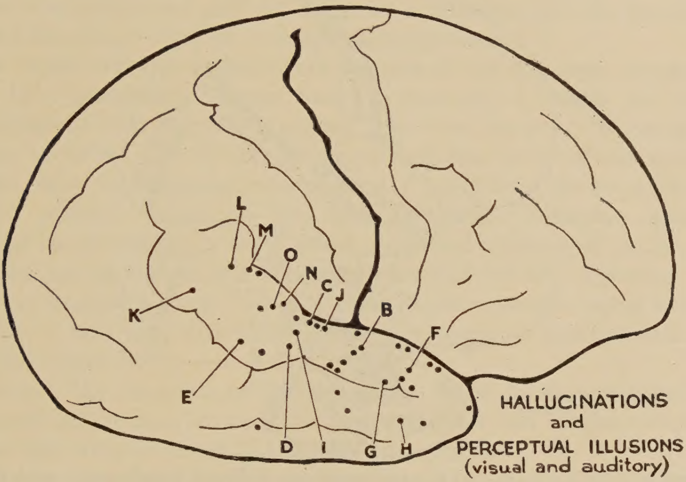

FIG. 1.—Summary chart of stimulation points (from unselected cases) producing psychical hallucinations (experiential responses) and illusions (interpretive responses). From Ferrier Lecture, Penfield, 1947.

Some years ago, in preparation for the Ferrier Lecture (Penfield, 1947), I reviewed 190 successive operations for focal epilepsy, all carried out under local anaesthesia. This included all the examples of such operations in unselected brain areas during a 9-year period. In 10 cases from that series stimulation produced "an experience that might be considered similar to Jackson's 'dreamy state.' "

These responses I called psychical and divided them into psychical hallucinations and perceptual illusions. The points of stimulation all fell on the temporal cortex as shown in Figure 1. No such responses were produced by stimulation elsewhere.

In the past eight years our understanding of temporal lobe seizures has advanced greatly, and there has been in the Montreal Neurological Institute a corresponding increase in the number of operations for this variety of epilepsy. Indeed the temporal lobe cases selected for surgical therapy now outnumber all others grouped together. With greater experience, we have learned to carry out deep stimulation with a coated electrode. By that method the superior and mesial surfaces are now often explored electrically, as well as the lateral and inferior surfaces.

The present conclusion is that psychical responses result from stimulation principally of the lateral and superior surfaces of either temporal lobe (Fig. 2). The superior surface is that portion of the temporal lobe that is hidden within the Sylvian fissure and in the circular sulcus that surrounds the insula beneath it. The mesial surface is made up of uncus and hippocampal gyrus.

The actual recording mechanism may be in the cortical grey matter where the stimulating electrode seems to awaken it or it may well be elsewhere, in areas which give no response to direct stimulation, such as the hippocampus and hippocampal gyrus. But if it is in such a zone there must still be specialized connections between that zone and the areas of temporal cortex in which stimulation does produce psychical responses. Either way, it is not going beyond the evidence to conclude that this area of cortex, which is marked "psychical responses" in Figure 2, must play an important role in the formation or preservation of the record of the stream of consciousness.

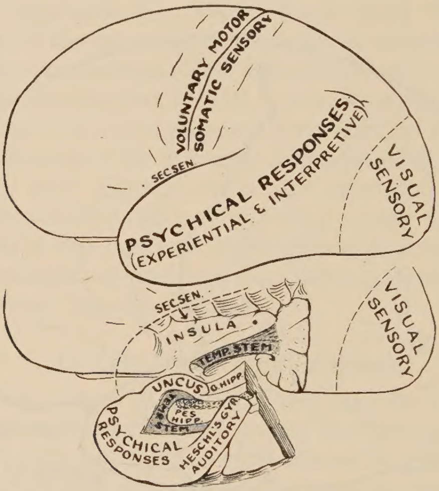

FIG. 2.—Chart of lateral surface of human brain and, below, a partial chart with the temporal lobe cut and turned down to expose the superior and mesial surfaces. Experiential and interpretive responses are most frequent on the superior and lateral surfaces. Furthermore, visual, auditory, somatic and second somatic sensation areas are indicated. "Temp. stem" indicates the white matter of the lobe which has been cut across.

## C. PSYCHICAL RESPONSES

Psychical responses to stimulation may be divided into two groups (1) *Experiential* and (2) *Interpretive*, thus corresponding with the psychical hallucinations and illusions that appear in temporal lobe seizures.

### 1. *Experiential Responses*

I will present certain examples of experiential response, without full clinical description, but using wherever possible the patient's own words as they were recorded at the time of operation.*

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* For those who might be interested, further information in regard to many of the patients cited in this communication may be found in the books and papers which I have published in this general field with various associates. A Patient Index, by initials, will be found in each of the books.

D.F. heard an orchestra playing a certain song when a point on the superior surface of the right temporal lobe was stimulated after removal of the anterior half of the lobe. The hearing seemed to her so realistic that she thought a gramophone had been turned on. The point was restimulated many times and each time she heard the same orchestra which seemed to begin playing at the same place in the same piece. When she was warned falsely, and stimulation was withheld, she heard nothing; when stimulated, with or without warning, she heard it. When she hummed, accompanying thus the music in her mind, the tempo was about what might have been expected of an orchestra.

The continued repetition of the stimulation seemed to facilitate this particular response rather than other possible responses. It was not a song that she knew very well and she could not recall when it was that she had "heard it that way before".

M.G. said, when the first temporal convolution on the right side was stimulated, "I hear people coming in—I hear music now, a funny little piece." Stimulation was continued and she went on to explain that the music she was hearing was the theme song of a children's programme.

S. Be—when various points were stimulated on the right temporal convolution: 16—"something brings back a memory. I could see Seven-Up Bottling Company." Then, after a pause, "Harrison Bakery." Warning without stimulation—nothing. 19—"I am trying to find the name of the song. There was a piano there and someone was playing. I could hear the song you know." 19 repeated without warning—This time he said, "someone speaking to another, and he mentioned a name but I could not understand it. 21—"Someone speaking to me in my left ear (contralateral) Sylvère, Sylvère.* It could have been my brother's voice." 25—"I seem to see someone—men and women—They seem to be sitting down and listening to someone but I do not see who that someone might be."

In general, the patient's awareness seems to be of an experience that is going forward but he is often not able to recall what had happened just before the incident nor what is about to happen following it.

L.G. saw a man fighting. When the point was re-stimulated he saw a man and a dog walking along a road.

A housewife G.F. heard her little son playing in the yard and was aware of the sound of automobiles passing.

J.T. exclaimed that he heard his cousins, who were actually in South Africa, talking. He was laughing, he said, at something with them and yet he knew at the same time that he was also in the operating room. Though he made the effort, he could not recall what they were laughing at.

A young woman exclaimed: "Oh, I had the same very, very familiar memory,—in an office somewhere. I could see the desks. I was there and someone was calling to me, a man leaning on a desk with a pencil in his hand."

## D. Record and Memory

These are all "strips" of experience. Sometimes the patient can recall the event. More often it has faded from recollective memory. But always it is familiar and he seems to be present and he acknowledges it as part of his own past. When music is heard, he may not be aware of its source or he may seem to be present in the theatre or church or café. He may re-experience the sense of enjoyment that came to him in that moment.

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* The hearing of his own name Sylvère repeated several times had been the aura that ushered in this man's seizures habitually, but for some years before operation the attacks had come without that hallucination and with no warning other than a sensation of nausea.

Because such phenomena can occasionally be produced by stimulation of the cortex of the temporal lobe I have suggested that the electrical current follows a pathway of facilitation that was formed during the original experience while other pathways remain closed to it. This is an hypothesis. Many years of work by physiologists and psychologists will be required to prove, disprove or replace it.

I suspect that nerve impulses pass from temporal cortex into the closely connected subcortical nuclei, along connections that were utilized during the time of the original experience. Indeed, I suppose that a part of the ganglionic machinery, that was involved in the understanding and the recording of detail in the stream of consciousness, is set in motion once more, repeating similar sequences of nervous conduction. The action of that ganglionic machinery might seem to constitute the very substratum of consciousness,* for the things that have been recorded are the things which once came within the spot-light of attention.

There is a very great difference between the stimulatory re-playing of a strip of record of the stream of consciousness and a voluntary act of recollection. It is obvious that, one minute after an experience, an ordinary individual can recall it voluntarily with a high degree of completeness. Unusual individuals can do so after longer intervals. Experiences which were surcharged with meaning or emotion may be recalled repeatedly and so remain available in considerable detail for a long time. But, in general, the record of routine experience passes quickly beyond our power of elective review. Most of it is lost to us forever, as far as voluntary recall is concerned.

Whether or not the methods of the psychoanalyst can re-activate the record with a completeness that rivals the electrode I have no means of knowing. I would suspect that the patient who is being analysed brings up a generalized memory, or one that has been modified by his subsequent thinking or subsequent experience. Electrical recall is quite different from this, since it often produces random samples of true experience, which may have no particular significance in the life of the patient.

Memory, as ordinarily defined, is something else. It includes so many generalizations and is so often progressively influenced by subsequent experience. Memory of a song or of a person may come in time to be a complete generalization assembled from a series of scattered experiences. The musician may call a song to mind or may play it or sing it from memory and yet be unable to recollect the circumstances of a single hearing of the song.

It is true that when a friend is seen by an individual after an interval of absence, or an old song is heard again, that one is apt to detect slight changes with astonishing accuracy and to make a judgment of familiarity or of alteration at once. It may well be therefore that each of the earlier experiential records of that person or song becomes available to the individual during the laying down of the new record. It is then that the new experience is interpreted and judgments of familiarity, strangeness, danger, distance, etc., are made.

### E. Temporal Lobe Seizures

Epileptic discharge, if localized and circumscribed, often produces a result which is similar to a stimulation response in the same area. Temporal lobe seizures,* produced by localized discharges, are often psychical in nature. They must be distinguished from the sensory seizures and motor seizures that are produced by discharge in other parts of the brain. But in order to interpret the phenomena encountered in temporal lobe seizures the clinician must realize that sensation and even movements may be produced by epileptic discharge which is not in the pre-central or post-central gyrus but deep within one Sylvian zone.

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* Jackson called this nervous action the most special of all the special nervous processes, the series evolved out of all the other lower series—"co-ordinations"—"reco-ordinated".

In the temporal lobe and in neighbouring structures deep within the fissure of Sylvius there are sensory areas. Thus discharge that originates in, or spreads to, these areas may give rise to sensations; for example, buzzing sound in Heschl's gyrus (Fig. 2), odours in the uncus, alimentary tract sensations in the insula, taste in the cortex just above the insula, somatic sensation from the "second sensory" area above the insula, and head sensations, and body sensations in the deep portion of the temporal tip. All of these phenomena may appear as auras or as integral parts of the unfolding pattern of a temporal lobe seizure.

When there is localized epileptic discharge in the areas of temporal cortex which, as already described, may give psychical responses to stimulation (Fig. 2) the result is a psychical seizure. Psychical seizures are of three kinds, (1) experiential, (2) interpretive and (3) amnesic as outlined in Table I. Perhaps it is more accurate to say that during psychical seizures there may be experiential, interpretive and amnesic phenomena since more than one of these three types of phenomena may appear in a single attack.

TABLE I

*Psychical Seizures or Dreamy States*

1. EXPERIENTIAL SEIZURE (psychical hallucination, "flash-back")
2. INTERPRETIVE SEIZURE (psychical illusion, déjà vu phenomenon, fear, etc.)
3. AMNESIC SEIZURE, AUTOMATISM (psychomotor confusion)

### 1. *Experiential Seizures*

The *experiential attack* is an hallucination of past experience. The patient may call it a flash-back or a dream. It is the same as the experiential response to stimulation that was discussed at the beginning of this address.

### 2. *Interpretive Seizures*

The *interpretive attack* is an illusion in regard to present experience; a false interpretation of the present situation.

During both types of attack the patient continues to be conscious and he is usually still capable of introspection. It is probably significant that these two forms of psychical seizure should come from the same general area. The first is a re-activation of the record of the stream of consciousness. The second is an altered interpretation of the recording that is being made at the moment.

Under normal conditions interpretations of present experience must depend upon a comparison of the present recording with similar past recordings. It is therefore not particularly surprising to discover that limited discharge in an area where past and present recordings seem to have some form of localization, disturbs the interpretation of the present experience.

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* It is important to recognize that temporal lobe seizures are extremely common. The focus of origin is most often in the superior and mesial surface of the temporal lobe including uncus and hippocampus. These are the areas that are hidden away from the surface.

The commonest causal lesion is *incisural sclerosis*. This is a chronic atrophic abnormality produced at the time of birth by herniation of the temporal lobe through the incisura of the tentorium, producing thus temporary occlusion of the anterior choroidal artery and adjacent arteries that cross the edge of the tentorium.

Although the ischaemic injury is produced during birth, the attacks may begin at any time within the first 20 or 30 years of life. For a general discussion of temporal lobe seizures, see Penfield, 1954a.

An interpretive seizure is an illusion, perhaps better called "illusory feeling", as suggested to me by Dr. Kubie. The following are the commonest varieties; a sense of false familiarity. This illusion is often called the "déjà vu" phenomenon. But the sense of familiarity usually applies to the total present experience including the sounds and the meanings of the moment as well as the sights. The patient may have the feeling that is opposite to familiarity, and report an illusion of strangeness, or absurdity; things seen or heard may seem to come nearer or to recede to a greater distance; a patient may experience a feeling of remoteness or a change in his own relationship to his environment.

Closely related to the interpretive seizures are *ictal* emotions*. It is as though these emotions were interpretations of the meaning of present experience. But all of these emotions may appear without his being afraid of, or lonely for, anything in particular. The patients have described these feelings with the words: fear, loneliness, sadness, scared feeling, terror.†

A few examples of interpretive seizures may be presented here.

*Case V.F.*

This man of 33 years suffered from attacks which were due to an atrophic discharging lesion deep in the right temporal region near the insula. He had been operated upon elsewhere and a small temporal excision carried out.

His attacks were as follows: (1) Dizziness. He felt as though he were whirling around. (2) Interpretive illusions of familiarity and of fear and also of seeing himself.

He said he was apt to have a strange feeling that all of this had happened before. It was, he said, as though he were in the "future listening to the past". It seemed that all this had happened before and he was then seized with a feeling of fear and was aware of a tight sensation in his stomach and rectum.

Attacks might be precipitated, when startled by a sudden sound, and especially by a heavy "cloying" perfume such as that at a perfume counter. On two occasions in the Hudson's Bay Company Store in Winnipeg, he had had an attack in the perfume department. He had learned also that it was perilous to ride on a bus where he might smell such perfumes on women passengers. Bad odours, such as that of gasoline or of a fish factory did not have such a precipitating effect!

These minor seizures might be followed by automatism and falling, with a brief interruption of consciousness, but major generalized convulsive seizures were rare. Following minor seizures there was a post-ictal right frontal headache.

At operation, under local anaesthesia, the right temporal lobe was exposed (Fig. 3). Deep electrical stimulation was carried out through point 10 (Fig. 4), using a unipolar electrode which was covered with an insulating coat except at the tip. Stimulation at a depth of 2 cm. along the superior surface of the temporal lobe, within the fissure of Sylvius, caused the patient to say suddenly, "That bitter-sweet taste on my tongue." He seemed confused and made tasting and swallowing movements.

The stimulating current was shut off and the electro-corticogram showed that a slow wave 4 per second generalized rhythm had been set up as an after-discharge. While this was continuing the patient exclaimed: "Oh God! I am leaving my body." Dr. Karagulla, who was observing him, said he looked terrified at the time of the exclamation and made gestures as though he sought help. When the electrocorticogram had returned to normal the patient seemed to be himself again. He was asked by the operator whether that had been like his habitual seizures. He replied, "A bit, Sir", then after a pause he added, "I had the fear feeling."

Stimulations in the temporal lobe deep to point 11 produced vestibular sensations. Once he said he was spinning around. Once he felt as though he were "standing up".

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* The word ictal is used to refer to the active phase of the attack, the period of discharge, without including the immediately succeeding period of ganglionic exhaustion.

† There may be an associated gripping sensation in the epigastrium or pupillary, pilomotor and pulse changes—phenomena which are controlled by mechanisms located at a distance. The patient's facial expression may suggest dread or terror, and his behaviour also. Other emotions, such as anger, ioy, pleasure, sexual excitement, have never been reported by our patients as results of local cortical seizure or cortical stimulation. I have not encountered any evidence of specific relationship of the human cerebral cortex to these forms of emotion.

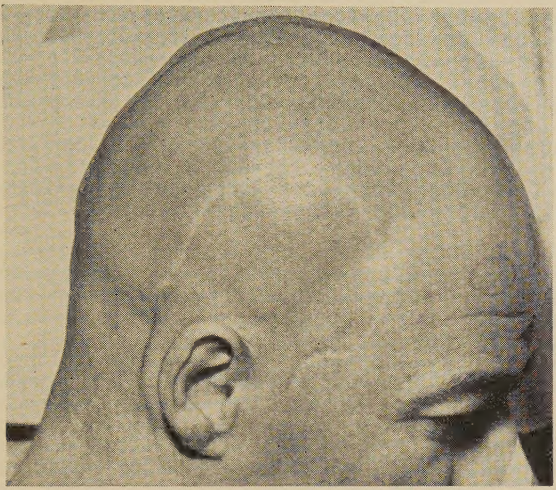

FIG. 3.—Case V.F. The patient is in position on the table ready for operation. Scar of former operation may be seen. See Fig. 4.

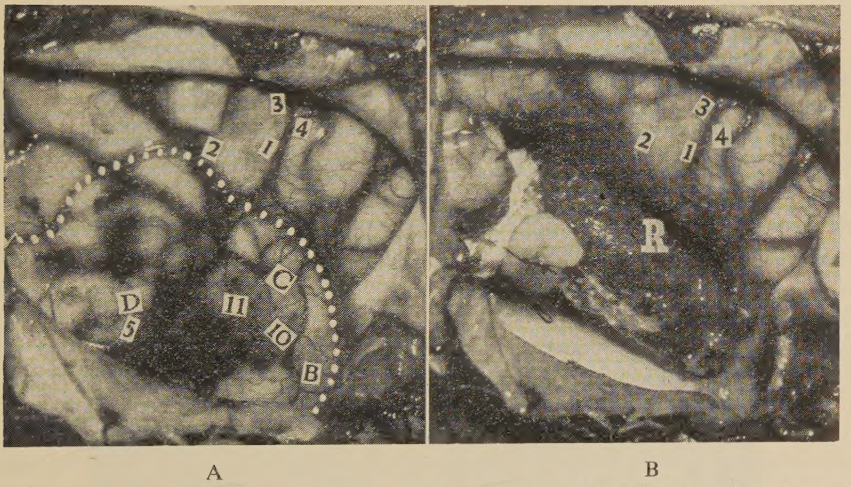

FIG. 4.—Case V.F. Craniotomy and exposure of right temporal lobe. Panel A shows the scar of a previous temporal excision which had been carried out elsewhere. Panel B shows the brain after the scarred anterior temporal lobe has been removed. R marks the exposed Island of Reil. The black thread over white gell-foam. demonstrates the method of closing off the inferior horn of lateral ventricle.

Tickets B, C and D in panel A indicate the area in which the electrocorticograph demonstrated "sharp wave" and "spike" abnormalities of electrical potential characteristic of epileptogenic areas. Stimulation at points 1 and 2 produced—opening of jaw, 3—sensation left side of tongue, 4—"floating" sensation referred to chest and abdomen. At 10 and 11, deep stimulation was carried out—see Text. The dotted white line indicates fissures along which excision was carried out.

In summary, this patient had, during minor seizures, a sensation of dizziness probably produced by discharge in or near the transverse gyrus of Heschl deep in the Sylvian fissure. This was followed by complicated psychical illusions, interpretive illusions, during which he felt an unjustified fear, a sense of familiarity, and an altered relationship to his own person as though he were outside of his body. These illusions were probably due to discharge in the superior surface of the temporal lobe anterior to Heschl's gyrus.

The record, at the time of stimulation, fails to state whether he experienced the illusory feeling of false familiarity then, but stimulation did produce the illusion of fear and of leaving his own body.

Electrical stimulation produced a vestibular sensation of whirling which resembled his initial aura. But it also produced something that could be considered more complicated than a sensory response, i.e. the feeling that he was standing upright. This might be considered a somatic illusion in the same class with visual illusions of distance.*

*Case W.S.*

A man of 30 years had had minor seizures for 5 years and major convulsive attacks for 3 years, evidently due to a traumatic injury of the left temporal lobe.

His minor attacks were as follows: (1) Thoracic sensation, (2) sounds seemed louder and faster, (3) thoughts or words came into his mind.

After the thoracic aura, if he was hearing a continuous sound, it would seem to become louder and if he was at work in the factory, the machinery seemed to be louder, the movement faster during such a seizure. Following that, "thoughts" came into his mind. But it was difficult to recall what the thoughts were. When he was asked if they were memories, he said, "No, they are more like words or combinations of words." He tried to explain by saying that it was like having a dictionary and having different words come to mind. At another time he said it was like thinking two things at once. At such times he would look around, he said, and know what was happening about him and yet the thoughts kept coming. This state was followed by confusion and automatism and after the automatism was over, some slight tendency to aphasia.

At operation there were dense subdural adhesions in the left Sylvian region due to an old subdural haematoma (Fig. 5). Stimulation at point 20 near the temporal tip caused him to have a small attack with thoracic sensation and "thoughts entering" his mind.

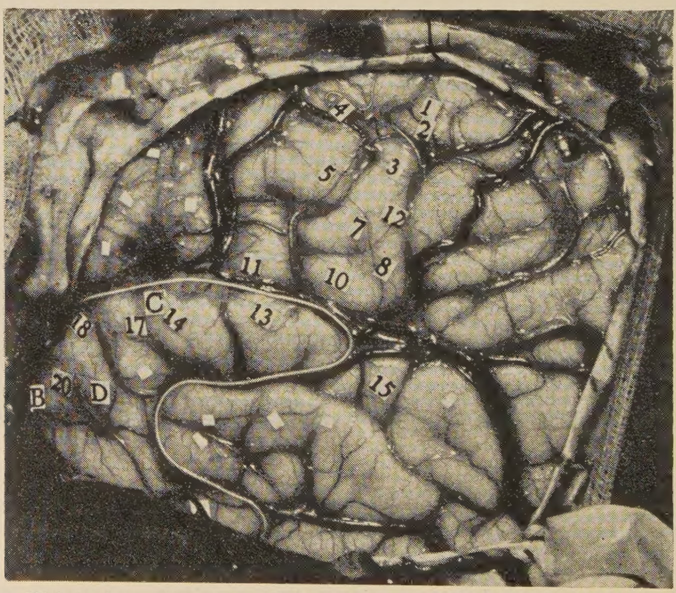

FIG. 5.—Case W.S. Left craniotomy carried out by my assistant Dr. John Hanbery. The white thread indicates the area of temporal lobe removed. B, C and D indicate electrographic abnormality. Stimulation produced responses: 4 and 5—movements of right mouth; 7 and 8—sensation in tongue; 10—swallowing; 11—sensation ("tiredness") in right leg and toe.—This is "second" sensory. It was repeated later, without warning the patient, with same result. 17 and 20—thoracic aura, perceptual illusion, hallucination of "thoughts".

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* Thus, it would seem that there may be interpretive illusions, regarding body position or body movement, which should be considered psychical rather than sensory. Other patients have made similar reports.

At 17, stimulation caused him to say, "I am going into a seizure." He was unable to speak and was automatic for a short time.

The change of interpretation of sounds which he described is a good example of an epileptic psychical illusion. It suggests that judgment of the intensity and the rate of sounds depends upon a neuronal mechanism that can be activated or disturbed by epileptic discharge or electrical stimulation. It is a change of interpretation. If there had been no sound he would not have been aware of the local discharge.

As a third phenomenon, thoughts or words came into his mind. This seemed to be a hallucination, always of the same type, but whether it was an experiential hallucination, which reproduced previous thinking, was never clear to the patient nor to us who studied his case.*

It is clear that these phenomena were produced by discharge in the superior surface of the left temporal lobe and it seems likely that automatism followed as the discharge spread into the amygdaloid area.

These experiential and interpretive seizures were described by Hughlings Jackson under the heading of "dreamy states" and he included with them attacks of automatism.† This brings the discussion to the third group of psychical seizures.

### 3. *Automatisms, Amnesic Seizures*

There is one constant characteristic of automatism; for the duration of each attack there will be subsequent amnesia. While in the automatic state the patient does not seem to be unconscious. But he has an alteration in consciousness which may be severe or slight. Thus he may seem to be completely, or only slightly, confused. He may move about aimlessly or he may have some apparent purpose, a purpose not easily influenced by his companions.

The one constant defect lies in the fact that the patient has lost the capacity of making a permanent record of his stream of consciousness. He has not lost all memory of the past, for he may find his way back to his home passing through city traffic during such an attack. He may even carry on, and complete, a previously prepared speech which he had begun before the onset of an attack of automatism, or he may play a well-known piece on the piano.

If the basic defect is an inability to record present experience, this would explain why the patient cannot interpret his present experience normally. It seems likely that interpretation of present experience is made during the formation of the new record or just after it is formed since it must be compared with the past records. The confusion is due to an interference with experiential recording and experiential interpretation. Electrographic studies prove that automatism appears with the onset of epileptic discharge and continues during the period of ganglionic fatigue that follows after the active discharge is over.

We can now localize the area in which epileptic discharge may produce temporal automatism (Feindel and Penfield, 1954). My associate William Feindel‡ restudied a group of patients in whom automatism was produced by electrical stimulation during operation. He found a remarkable concentration of points in the vicinity of the amygdaloid nucleus (Fig. 6). This is about 4 cm. posterior to the tip of the temporal lobe and 4 cm. deep to the lateral surface.

Stimulations that produce automatism are usually, if not always, followed by after-discharge. That is to say, there is a brief continuation of confusion and amnesia after cessation of stimulation. We have assumed that the stimulation itself, or the local seizure discharge, fires inward along more centrally located tracts so as to interfere centrally with ganglionic nuclei which are involved in the process of experiential recording in both temporal lobes.

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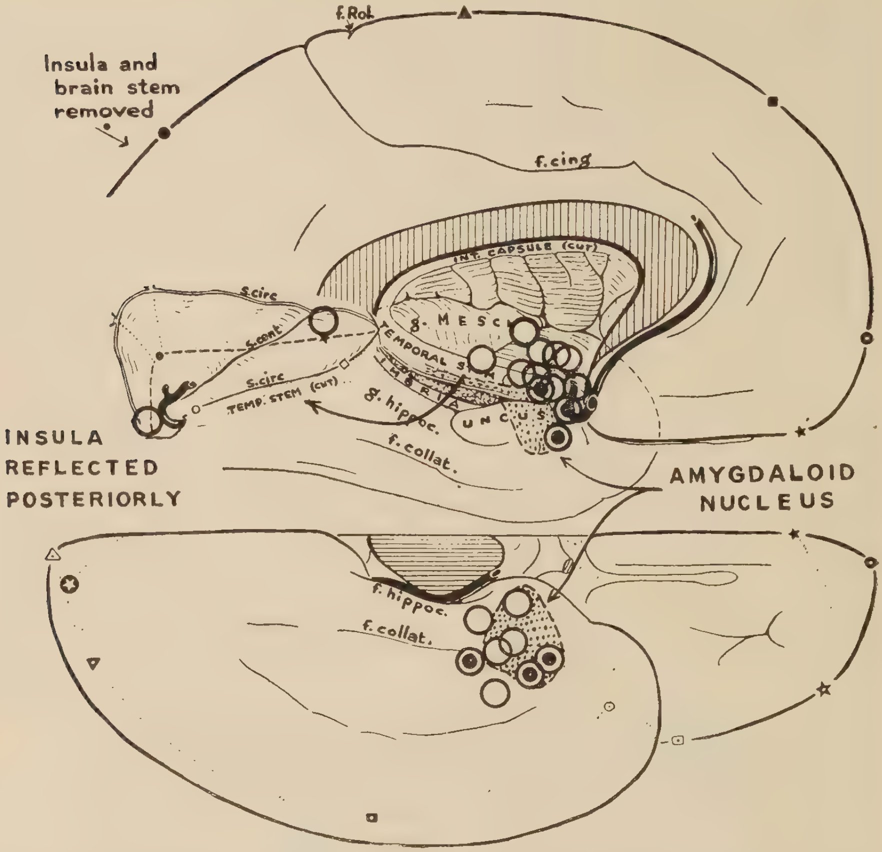
* The thoughts that may force themselves into a patient's mind during this type of seizure are discussed elsewhere, Penfield, 1955.

† The dreamy states were subsequently called psychomotor seizures by Gibbs, Gibbs and Lennox (1937) who described the frequent association with them of 6 per second disturbances of electro-encephalographic rhythms.

‡ A study of automatism and the localization of the discharge and the electrical stimulation that produces it will be made shortly (Feindel and Penfield, 1954).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f. hippoc.
f. collat.

FIG. 6.—Stimulation points which produced primary automatism shown on the mesial and inferior surfaces of the brain. The projection of the amygdaloid nucleus to the surface is shown by the dotted area. The insula has been removed in the mesial view and is shown rotated posteriorly (after Feindel and Penfield, 1954).

## F. DISCUSSION

Hughlings Jackson pointed out that clinicians must provide "facts bearing on the physiology of the mind" since they alone "witness the results of experiments of disease on the nervous system of man". The facts which he reported 75 years ago are still facts. He also set for us a brilliant example of rationalization, spinning hypotheses from the threads of his observations made in the wards of the National Hospital at Queen Square. Some of those hypotheses stand today as established principles. Others have been discarded but all of them served useful purposes.

Before discussing the meaning of these phenomena it would be well to restate certain facts in summary.

(*a*) Stimulation of the temporal lobe of patients subject to focal epilepsy may produce re-enactments of previous experience in astonishingly complete detail.

(*b*) Similar stimulation may alter the patient's interpretation of present experience (interpretive illusion).

(*c*) Stimulation, which causes after-discharge beneath the uncus and in the peri-amygdaloid area, results in primary automatism during which there is complete interference with the recording of the patient's current experience.

All three of these results of stimulation may be produced also by spontaneous epileptic discharge if it is local.

The first two (*a* and *b*) are positive phenomena. That is to say, there is activation of a functional mechanism. In the first case the activation consists in the "re-playing" of a "strip" of experiential record. In the second case it consists in alteration of the interpretation of the new "strip" of record that is being formed during the time of the stimulation.

The third phenomenon, automatism, is not an activation in a functional sense. It is an interference with the normal process of experiential recording. When the electrode is withdrawn the interference continues for a little time. This suggests that local interference with the grey matter of the peri-amygdaloid area is not enough to produce the effect. There must be interference with the function of more centrally placed, but intimately connected, ganglionated areas.

Before discussing the experiential record further, let me repeat what was written in an earlier section of this paper:

"It seems reasonable to suppose that the ganglionic record is complete, and that it really does include all periods of each individual's waking, conscious life." This is a supposition that could never be proven. Some periods of time may be lost. But it is clear that the portions of the strip which are activated do represent to the individual those things of which he was aware during a certain period of time, and he feels that nothing is missing. Successive experiences are presented to him in proper sequence and at a rate which seems to be the same as that of the original experience.

Since a volley of electric pulses applied to a point on the temporal cortex produces this effect I would hypothecate that the electrical activation is following a ganglionic pathway, as already explained, and that that pathway was formed in the first place by a succession of impulses or a stream of neuronal activity that emerged from that zone in the brain in which final neuronal integration is possible. Call it for the moment the zone of central integration.

Where is this pathway that holds in its turnings the record of the past? It seems unlikely that any delicate or complicated function would be possible within the area of grey matter that is being stimulated, considering the relatively large zone that must be under the direct influence of the electrode. There must be blockage or inhibition of transmission from the area except along one line of neurone communication. This would allow passage of a single stream of impulses away from the stimulated zone and into some other ganglionic region where the single "strip" of the record can be activated, free from the confusing influence of the electrical state that surrounds the electrode.

This line of reasoning suggests the possibility that the recording pathway is located elsewhere in the temporal cortex or, as seems more likely, in a closely associated zone of grey matter such as the hippocampus.

The pathway is, it may be supposed, no more than a sequence of ganglionic connections. This sequence must be the same as that which was followed by the stream of neurone impulses which emerged from the zone of central integration at the time of the original experience. The pathway therefore is a trail of facilitation, permanent facilitation of each cell or dendrite or synapse, through which the original experiential stream of impulses passed.

There is evidence, that has been elaborated elsewhere (Penfield, 1938, 1952, 1954b), that the most important area of integration is not to be found in association systems of the cerebral cortex, but in a more centrally placed area within the higher brain stem. It must be assumed that there is in this area a central or centrencephalic integrating system into which the afferent streams of the sensory pathways pass and from which the efferent stream of impulses emerges that results in voluntary action.

Hughlings Jackson assumed that such an area must exist. He called it the "highest level", the place where final re-representation occurred. But it would be stupid of us to assume that he believed in independent function at any level.

On the contrary, centrencephalic integration must be the outcome of synchronous central and cortical activity; activity in the brain stem and in those areas of cortex of either hemisphere whose function is suited to the changing requirements of the moment. It seems likely that the temporal lobes are used simultaneously, as though in duplicate, for the purposes of recording the stream of consciousness.

To return to the question of the formation of the record, it has been pointed out that it contains only those things of which the subject was aware in the interval of time during which the record was formed, those things to which he paid attention.

One may suppose that it is in this centrencephalic system that the selection of the content of consciousness is made. There, all those things of which an individual is aware may be formulated and expressed in a complex of neurone activity. That complex might be conceived of as a succession of nerve impulses that is projected outward in such a pattern that it forms the appropriate ganglionic sequence which creates the record of the stream of consciousness.

The pattern of the passage of that sequence through neurone connections, probably in some portion of the temporal lobes, is made permanent by facilitation. The conduction facilitation in that pattern is the record, the "strip", of the stream of consciousness. This is an hypothesis that would seem to fit the facts. It depends upon assumptions similar to those in the current conception of what happens in the central nervous system during the process of learning.

The final action of integration within the brain constitutes the neuronal mechanism of the mind. The original formation of the ganglionic record, in which the temporal lobes play such an important role, must constitute a part of this mechanism.

There may well be secondary employment of the record during voluntary recollection and in the process of recognition of familiar things. But, as has been pointed out above, memory comes to be a generalization while the record remains unaltered by subsequent experience.

In addition to that it is evident that the cortex of the temporal lobe plays an active role in the interpretation of present experience and the comparison of present with past experience. Stimulation or epileptic discharge in that same general area of temporal cortex (psychical responses, Fig. 2) may produce this second type of psychical phenomenon. It is as though some of the neuronal machinery that is normally employed in the interpretation of current experience is located here in the same general area in which the experiential record can be activated. One may assume that judgments are made normally while the original record is being formed and that the new record is thus compared with the past.

The sense of familiarity ("déjà vu") is an interpretation—it might be called a feeling or even an emotion—which accompanies new experiences. It is a reaction which is set off very easily in some patients and, it should be added, in some individuals who are not subject to overt seizures. The reaction may have the same character regardless of the nature of the experience.

The feeling of absurdity, or unfamiliarity, is a contrary interpretation but a reaction of the same order. Distortion of judgments of size, distance, and loudness are likewise of the same order. Similarly, such illusions may have to do with the relationship of the individual to his environment, described as being far away, out of this world, lonely. Feelings that are called emotions are similarly produced the most frequent being fear, nameless dread or specific menace which may or may not be associated with tears, panic, dilatation of pupils.

All of these things might be considered interpretations. They must be caused by more or less specific neuronal reactions or reflexes which serve a useful purpose under normal conditions but which may become habitual responses in states of chronic epileptic discharge located in temporal regions.

One might well question whether habitual misinterpretation of current experience may be related to disturbances of behaviour. It is our impression that disturbances of behaviour are more frequent among temporal lobe epileptics than in other groups. It is likewise our impression that successful removal of a discharging temporal focus sometimes results in behavioural improvement. However this is an aspect of temporal lobe activity regarding which no statistical conclusion has as yet been reached in our clinic.

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# THE HYPERVENTILATION SYNDROME*

By

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## INTRODUCTION

THE hyperventilation syndrome is the name given to a distinctive group of symptoms and signs which are caused by an increase in the depth and rate of breathing. This abnormal breathing is nearly always the result of emotional stress.

The association between emotional stress and disorders of breathing is well known: sighing with grief, gasping with rage, panting with fear, heaving with resentment. Of its origin, Darwin said, "Men, during numberless generations, have endeavoured to escape from their enemies by headlong flight, or by violently struggling with them; and such great exertions will have caused the heart to beat rapidly, the breathing to be hurried, the chest to heave and the nostrils to be dilated . . . And, now, whenever the emotion of fear is strongly felt, though it may not lead to any exertion, the same results tend to reappear through the force of inheritance and association."

Cannon (1920) described hyperventilation as a preparation for flight or fight:

"The forced respirations in deeply emotional experiences can be interpreted, therefore, as an anticipatory reduction of the carbon-dioxide in the blood, a preparation for the augmented discharge of carbon-dioxide into the blood as soon as great muscular exertion begins."

Primitive man could and did take to his heels or use his fists if afraid. Modern man, inhibited by cultural and social traditions of behaviour, is unable to do so. So the age-old physiological preparation for flight or fight is not carried over into any functional motor activity. This is when trouble arises. A strong emotional reaction with no motor outlet turns on itself to cause physical upset.

In this paper a study is made of the symptoms and signs by which to recognize this syndrome, and of some of the physiological mechanisms which are brought into operation.

## HISTORICAL REVIEW

The first description of the effects of overbreathing in man appeared as a footnote to an article by Haldane and Poulton (1908), the physiologists. They used forced breathing on themselves during experiments on the effect of want of oxygen on respiration, and the footnote comments: "Poulton, after about a minute of forced breathing, began to feel tingling in the hands and to a less extent in the feet. This became very painful, the pain reaching a maximum usually about half a minute after the apnoea had begun. The tingling was accompanied by numbness and sweating of the hands and a peculiar sense of giddiness and abnormality almost resembling the effects of anoxaemia. Except for the feeling of abnormality these symptoms were absent in Haldane even after 5 minutes of forced breathing." They mentioned that forced breathing had been used to produce partial anaesthesia for slight operations and attributed the disturbance of consciousness to loss of carbon dioxide. "Deficiency of $CO_2$ appears to produce a condition of diminished excitability; but the explanation of the tingling sensations is by no means clear." They were impressed by the apnoea following overbreathing and mentioned that Cingalese pearl divers hyperventilated before diving as a form of religious ceremony. Poulton demonstrated to the Physiological Society the effect on himself of forced breathing. During the period of apnoea "some of those present thought that something was wrong with Poulton and could hardly be restrained from performing artificial respiration. One or two of them were so much affected that they became faint or sick and had to retire hastily. The face gradually assumes the leaden corpse-like hue of great anoxaemia and it may be about a minute after this change begins before any desire to breathe is experienced."

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* Thesis awarded M.D., Cape Town.

Henderson (1909) made a study of the effects of overbreathing. He hyperventilated sixty subjects for 45–90 seconds and concluded that the effects were similar to those of shock. He, too, was impressed by the apnoea, and warned that it might be a danger in prolonged overbreathing. He cited experiments on anaesthetized dogs, where, he said, 25–30 minutes of artificial respiration led to apnoea so prolonged that the heart failed after 7–8 minutes from lack of oxygen. He considered that apnoea almost invariably followed overbreathing and found it absent in only two or "possibly three" of his sixty subjects. Symptoms following overbreathing were more severe in these people. There appears to have been a tacit assumption by all subsequent workers that the majority of subjects after overbreathing experience this cessation of breathing during which time the $CO_2$ of the alveolar air is built up again. It was not until 1946 that Mills, describing the respiratory pattern after 1–1½ minutes of overbreathing in thirty-five subjects selected at random, found that only ten of these showed apnoea fairly consistently after hyperventilation. Eight of his subjects continued to overbreathe, often with great vigour. The remaining 17 showed an intermediate picture. Mills could not find any obvious physiological reason for the hyperpnoea of eight of his subjects and concluded that "it results directly from that same cortical activity which is initially responsible for the forced breathing".

The circulatory derangements after overbreathing were again emphasized by Hill and Flack (1910). They found that "polygraph tracings show acceleration and enfeeblement of the pulse during forced breathing; the pulse can be felt to become weak or even disappear with each inspiratory effort, to return with expiration. Systolic blood pressure falls considerably with each inspiration." In 1928 Vincent and Thompson investigated blood pressure changes during overbreathing. They found that 90 per cent. of people showed an average fall of 25 mm. of Hg in systolic pressure. The remainder showed an average rise of 37 mm. Hg. The only difference between the two groups was that the subjects whose blood pressure rose had very slow initial pulse rates. In 1938 Soley and Shock made an interesting observation: "We have been impressed by the peripheral vasoconstriction, which is so marked during forced breathing that the fingers must be stabbed deeply to obtain blood for chemical studies." Kety and Schmidt (1946) did continuous blood pressure readings and measured cardiac output in five volunteers. They found that the blood pressure did not fall, in fact it tended to rise in some cases, though not significantly. Cardiac output was reduced 11 per cent. during passive hyperventilation, but during active hyperventilation it was maintained by a constant tachycardia.

The neuromuscular effects of overbreathing were first noted by Vernon (1909). He had suggested that divers might remain under water for 9–10 minutes by combining oxygen inhalation with hyperventilation and utilizing the subsequent apnoea. On trying it on himself he was struck by the fact that after 6 minutes of overbreathing his hands passed into a condition of tonic rigidity and for the first 1½ minutes of the subsequent apnoea were "completely paralysed".

More than 10 years passed before the clinical importance of this observation was realized. Then Grant and Goldman (1920) recognized that many of the symptoms and signs following overbreathing corresponded with those of tetany. The fact was driven home to them in a dramatic fashion during an experiment with Goldman as the subject. Grant describes it thus: "After breathing very deeply for 30 minutes A.G. suddenly went into a complete tetanic convulsion. At the onset he involuntarily gave a loud high-pitched scream, probably due to contraction of the muscles of respiration and forcing of air out through contracted vocal cords. The entire body was rigid, all the muscles being contracted in tetanic spasm. The back was arched somewhat and all extremities extended completely. Relaxation occurred within 30 seconds, and there was no further spasm." They also noted, unlike Vernon, that the tetanic spasm could be overcome by an act of will, and mentioned that this is also possible in the spasm of idiopathic tetany.

The next step was to explain the pathogenesis of this tetany of hyperventilation. Grant and Goldman thought that it was primarily due to an alkalosis in the body. The reduction of $CO_2$ in the alveoli by overbreathing caused a reduction of $CO_2$ in the blood. This disturbed the $H_2CO_3$:$NaHCO_3$ ratio and produced an alkalosis, because $CO_2$ is washed out of the blood more rapidly by overventilation than $NaHCO_3$ is decreased by excretion or other means.

Although they considered the alkalosis to be of primary importance they also attempted to find a link with the familiar tetany of hypocalcaemia. Serum calcium levels in their cases were normal, so they suggested that when the "$CO_2$ of the blood is reduced by overventilation, a portion of the calcium is in some way rendered inactive though still present in the circulating blood".

Estimation of serum calcium appeared as almost a routine investigation during experiments on hyperpnoea after this. The only workers who claimed a significant calcium change were Barnes and Greaves (1936), who found a diminished calcium level in the cerebrospinal fluid after overbreathing. Their work was promptly refuted the following year by McCance and Watchorn (1937), and independently by Cumings and Carmichael (1937). All subsequent workers agreed that the serum calcium level either remains unchanged during hyperventilation (Schultzer and Lebel, 1939; O'Donovan, 1943), or shows a slight rise (Fowweather, Davidson and Ellis, 1940). Fowweather *et al.* reported a marked drop in phosphate levels in the blood immediately after overbreathing but this work has not been confirmed.

During the year that Grant and Goldman's article appeared, Collip and Backus (1920) were also occupied with the cause of the symptoms of overbreathing. They found that during hyperventilation the $CO_2$ tension of the alveolar air fell 44 per cent. and the $CO_2$ combining power of the venous blood fell 14·3 per cent. They also noted that the acidity of the urine was markedly decreased, a diuresis occurred and the rate of elimination of phosphates was increased. Their conclusions were that development of definite tetany and "muscle cramps" in many subjects during hyperpnoea was due to an alkalosis of the tissues. Alkalosis is today a well-recognized cause of tetany and the tetany following hyperventilation is generally accepted as being due to an alkalosis produced by the "washing out of carbon dioxide" from the blood.

In 1922 Goldman made a further significant contribution by showing that some people hyperventilate involuntarily, thus producing symptoms. He gave the credit for the first description of such a case to Barker and Sprunt (1922) who described involuntary overbreathing with tetany production in a patient convalescing from epidemic encephalitis.

The first of Goldman's eleven cases was a medical student who, during an attack of gall bladder colic, involuntarily hyperventilated and found that this lessened his pain. In subsequent attacks he deliberately overbreathed to achieve this analgesic effect. He diagnosed the cause of his ultimate tetany himself, as he had often seen Goldman demonstrate the effect of hyperventilation during lectures. Five cases were students who had become tetanic during a class fight and in them Goldman attributed this to excessive hyperpnoea following the acidosis of violent exercise. Two cases had acute infections with upper respiratory tract symptoms and one case had abdominal distension and vomiting. The remaining two cases were hysterical and Goldman's comment was that "some cases of hysterical pseudotetany are undoubtedly real cases of tetany due to over-respiration".

It was only several years later that it became clear that involuntary hyperventilation in otherwise healthy individuals was usually the result of emotional stress. In 1929 White and Hahn drew attention to the symptom of "sighing dyspnoea" and described it as a valuable indicator of nervous tension. In 1934 Baker describing several cases stressed the importance of "sighing dyspnoea" as a manifestation of emotional stress. The same year Maytum and Willius (1934) recognized sighing dyspnoea as a form of hyperventilation. The following year Christie (1935), describing neurotic respiratory patterns, claimed that patients with conversion hysteria characteristically complained of "an inability to get enough air into the lungs so that in mild cases deep sighing respirations were characteristic while in severe cases a paroxysm of hyperventilation leading to hyperventilation tetany might occur". In 1942 Silverberg emphasized the importance of careful history taking in patients complaining of dyspnoea because in this way the breathing difficulty resulting from emotional stress could be readily differentiated from that of organic disease. Although healthy individuals occasionally hyperventilate because of heat—Bazett and Haldane (1921), Wingfield (1941) and Dibden (1949)—or because of excessive overbreathing after exertion—Goldman (1922) and Dibden (1949)—most people do so as a result of emotional stress.

The effects of hyperventilation on the neuromuscular system led Rosett (1924) to advocate overbreathing as a simple, harmless technique for unmasking central nervous system disease. He took the view that the main effect of hyperventilation was on the cerebral cortex. "In disease of the cerebrum the manifestations referable to the particular system involved become vastly exaggerated under hyperpnoea. In injury of the pyramidal system, so slight as to escape detection by ordinary means, definite signs and symptoms are observable. Every form of abnormal involuntary movement referable to disorder of the striatal system becomes exaggerated to the greatest possible extent. Mental abnormalities assert themselves in pronounced abnormal behaviour." Hyperventilation is still used nowadays in an attempt to render doubtful neurological signs, for example an equivocal plantar response, more definite.

The individual susceptibility of people to the effects of hyperventilation was emphasized by McCance (1932). He reported the cases of two women who "with scarcely noticeable overbreathing" went into tetanic spasm. He could not find any cause for this phenomenon. In 1939 Schultzer and Lebel again drew attention to the "hypersensitive type" and in 1943 O'Donovan described these people as individuals who, breathing at the rate of 55–60 breaths a minute, develop tetany in less than 2 minutes or who experience such severe symptoms within 2 minutes as to prevent them from continuing overbreathing. O'Donovan was inclined to think that a predisposition to alkalosis could be induced "so that with each hyperventilation the nervous system becomes more easily excited and responds in an increasing degree until tetany appears with a relatively small stimulus". He claimed that in some cases this hypersensitivity could be abolished by vitamin D or other hypercalcaemic therapy.

The clinical concept of hyperventilation was extended by Kerr, Dalton and Gliebe (1937) who introduced the term "hyperventilation syndrome" to cover the many symptoms which had been observed in patients who overbreathed involuntarily. They recognized that emotional stress lay at the root of the syndrome in most cases and made the important point that patients seldom presented with tetanic spasm but commonly did so with rather vague ill-defined symptoms. There is a risk here, however, of widening the concept too much and obscuring the fact that hyperventilation involves definite mechanisms which set a limit to symptoms and signs. Kerr *et al.* seem to have identified the hyperventilation syndrome with the anxiety state. It is significant that the following year Soley and Shock (1938) attributed all the symptoms and signs of "effort syndrome" to hyperventilation.

In 1938 a useful contribution came from Fraser and Sargant, who described twenty cases of "hyperventilation fits" and differentiated them from hysterical and epileptic seizures.

In 1940 Fowweather, Davidson and Ellis thought that there was much justification for the term hyperventilation syndrome. They sought to explain the wide variation in clinical symptoms and signs by a tissue alkalosis which manifested itself in tetany in those individuals whose voluntary musculature was particularly susceptible, or in "effort syndrome" in those whose circulatory systems were susceptible and so on.

Later many workers thought that the term hyperventilation syndrome was being used to include too much. Guttman and Jones (1940), Wood (1941) and Friedman (1945) agreed that effort syndrome could not be wholly explained by hyperventilation. The fact remains, however, that the Kerr school has made a valuable contribution in (to quote Gliebe and Auerback, 1944) emphasizing hyperventilation "as an important mechanism of psychosomatic disease—it demonstrates one means whereby emotional disturbances can produce physiological and biochemical changes and physical symptoms".

World War II focussed attention on the occurrence of the hyperventilation syndrome among aircrew. Boothby, while learning to fly, experienced distressing symptoms which he afterwards recognized were due to overbreathing and, in collaboration with Hinshaw (1941), investigated the effects of hyperventilation on co-ordination and cerebration. They suggested that the phenomena in pilots of "blacking out" and "freezing to the controls" might in some cases be due to overbreathing. Hyperventilation at low altitudes was due to emotional stress; at high altitudes oxygen lack was an additional factor. Carryer (1943, 1947) was another investigator who emphasized the importance of hyperventilation in aviation medicine.

With increasing recognition of the syndrome the various specialities began to contribute knowledge of its manifestations in their own particular fields.

That hyperventilation could produce inversion of T waves in the electrocardiogram was shown as early as 1932 by McCance. This became of increasing importance later because the combination of praecordial pain (not uncommon in the hyperventilation syndrome) and electrocardiographic changes led to the erroneous diagnosis of myocardial infarction in anxious patients. In 1943 Thompson demonstrated marked electrocardiographic abnormalities, consisting either of late inversion of T or of S–T depression with marked lowering of T in any or all leads of the electrocardiogram during overbreathing in patients with normal hearts. They thought that alkalosis was the main factor in causing these abnormalities. In 1946 Christensen reported sinus tachycardia, depression of S–T segments and iso-electric, diphasic or inverted T waves during overbreathing. He explained them as resulting from an interference with coronary blood flow "by increased intramyocardial tension due to hypocapnia". In 1947 Scherf and Schlachman described lowering of R and T waves in lead 1. They stated that "as long as a marked increase in heart rate was avoided and the respirations were not sufficiently rapid and shallow to cause anoxia, no depression of the RS–T segment was observed". They thought that the changes which did occur resulted from positional changes of the heart.

The co-existence of organic heart disease and hyperventilation was stressed by Stead and Warren (1943) who described patients with compensated heart disease whose "dyspnoea" was wrongly attributed to congestive heart failure.

In 1946 Herxheimer reported that asthma could be precipitated in susceptible subjects by overbreathing. He suggested that it might play a part in the pathogenesis of psychogenically triggered asthmatic attacks.

In 1947 McKell and Sullivan found that 5·8 per cent. of consecutive ambulatory patients with gastrointestinal complaints were in reality suffering from the effects of the hyperventilation syndrome. They suggested that anxious patients often got a feeling of fullness which imitated air-swallowing. "This interferes to some extent with the respiratory rhythm and seems to initiate the hyperventilation in some cases."

Engel, Ferris and Logan (1947) reviewing the subject, stated that "hyperventilation may occur as a more or less non-specific reaction to the experience of terror, extreme anger, severe pain or other intense emotions in essentially healthy individuals or it may be a symptom of neurosis". They divided the symptoms resulting from overbreathing into two more or less separate groups—one related to the reduction in consciousness and one related to the tetany. They found that there was a close correlation between the "degree of slowing of frequency of the encephalogram and the degree of reduction of awareness". They thought that the symptom of tetany had received an undue amount of attention and that the "reduction in consciousness develops much earlier and is much more disturbing to the patient".

In 1949 Dibden reviewed the subject very fully and stressed the importance of recognizing the syndrome because "the dramatic demonstration of the nature of the syndrome symptoms by a hyperventilation test so impresses the patient as to create an excellent rapport with the psychiatrist".

In 1950 Rice claimed that during 1,000 routine interviews 10 per cent. of patients complained of symptoms and signs of the hyperventilation syndrome. He described the symptoms in detail and discussed their pathogenesis.

The present position is, that overbreathing is recognized as a cause of disturbing symptoms; that involuntary overbreathing is a definite clinical entity; that a wide variety of symptoms and signs have been grouped under the term hyperventilation syndrome; and that the most common cause of this syndrome is stress.

## Symptoms and Signs

### Clinical Symptoms and Signs

This series comprises forty patients who were seen during a two-year period at Groote Schuur Hospital. They were referred for investigation from wards or out-patient departments. Most of them came from the neuro-psychiatric or medical departments. Two came from surgical wards.

Ten cases were actually hospitalized because of the hyperventilation syndrome (though not diagnosed as such on admission); five cases manifested symptoms and signs of the syndrome while in hospital for other complaints; and twenty-five cases were referred to the out-patient departments with a variety of diagnoses.

*Age*

The oldest patient was 54 years, the youngest 17.

Average age was 30·9 years.

| | |
|---|---|
| Under 20 years | 10 patients |
| 20–29 years | 7 patients |
| 30–39 years | 12 patients |
| 40–49 years | 8 patients |
| 50 years and over | 3 patients |

*Sex*

Twenty-seven females. Thirteen males.

*Race*

Thirty-five Europeans. Four Coloured. One Malay.

Clinically almost all systems of the body were involved. Symptoms and signs are described and discussed under each separate system.

### Respiratory Symptoms and Signs

*Symptoms*

Twenty-four patients complained of respiratory difficulty, but in only one of them was it the main complaint. Many did not mention it unless asked directly. Only three patients realized that they were overbreathing. The characteristic description of the respiratory difficulty was, "I could get air into my chest but felt unsatisfied", or, "I felt that I could not get a deep enough breath". Associated with this sensation there was often a feeling of being shut in or oppressed. Patients complained that the chest felt "tight" and they felt that they must get fresh air. In some cases this led to extraordinary behaviour: one man drove through town holding the door of his car open, "to let in all the air"; a woman always rushed out of her house, whatever the hour, if she got an attack, "because I felt I would die for lack of air"; another patient tore open his collar "to let all the air in".

Two patients complained of "panting for breath" during attacks. One complained that she yawned excessively and when a hyperventilation test was done on her she began to yawn uncontrollably after 30 seconds.

Two patients complained that they got a stuffy feeling in the nose at the onset of an attack and were forced to breathe through the mouth. During hyperventilation tests the majority of the subjects automatically breathed through the mouth.

Previous "respiratory conditioning" was seen in three patients; one of them said, "My wife is asthmatic and watching her struggling for breath makes me feel that I can't get enough air"; another woman said, "My attacks started just after my child died from a gland bursting in her throat and suffocating her"; a third said, "I have a congenital heart and doctors are always asking me about my breathing."

The respiratory difficulty might come on at any time but occurred most frequently when the subject was tired or upset, in a crowded place, or preparing for sleep. Five subjects were actually awakened from sleep by respiratory difficulty and occasionally the marriage partner would awaken the heavily breathing subject "before an attack developed".

The characteristic and striking feature of the respiratory difficulty was that it was never related to exertion. If it appeared to be so related, questioning always revealed that it occurred either after or before—never during exertion. Indeed, in some cases it was actually relieved by some form of physical activity and many patients said, "When I got the trouble with breathing I was restless and had to walk up and down, and that seemed to help me."

The patient in whom the respiratory difficulty was the chief complaint was a man of 45 years, who said that three or four times a week during the previous year he had been getting attacks when he "could not get a proper breath". This woke him from sleep and he would jump out of bed contorting his body grotesquely in search of respiratory satisfaction. Sweat poured off him, his abdomen became distended and he felt giddy. Attacks lasted about 30 minutes.

Fifteen patients denied any respiratory difficulty.

Interestingly enough seven of these had gross hyperventilation attacks while under observation in hospital. Even at this time they denied any breathing difficulty. An eighth was instructed to overbreathe and promptly developed one of her "fits". Her mother, who was watching the procedure, said, "Oh, she always breathes like that during an attack but I did not think it important enough to mention in the history."

Two patients said that they did not notice anything wrong with the breathing, "but my friends always know when I am going to get an attack because my breathing gets so deep".

No independent evidence was available of the breathing during attacks of the remaining five patients in this series.

Goldman (1922) claimed that a person must double his respiratory volume before becoming conscious of his breathing. McCance (1932) reports two cases where "with scarcely noticeable overbreathing tetany was induced".

### *Signs*

Chronic irregularity of breathing was found in two of ten patients of whom respiratory tracings were taken (Fig. 1 (*a*) and (*b*)).

Hyperventilation took the form of:

1. Deep, fairly rapid breathing. This was the common type. Subjects usually opened their mouths at this time.
2. Very fast, shallow breathing or panting. This was seen in only two cases. It should be noted that when patients were told to "pant" their breathing was still usually deeper than normal.

(Type of breathing after hyperventilation—see Experimental Section, page 488.)

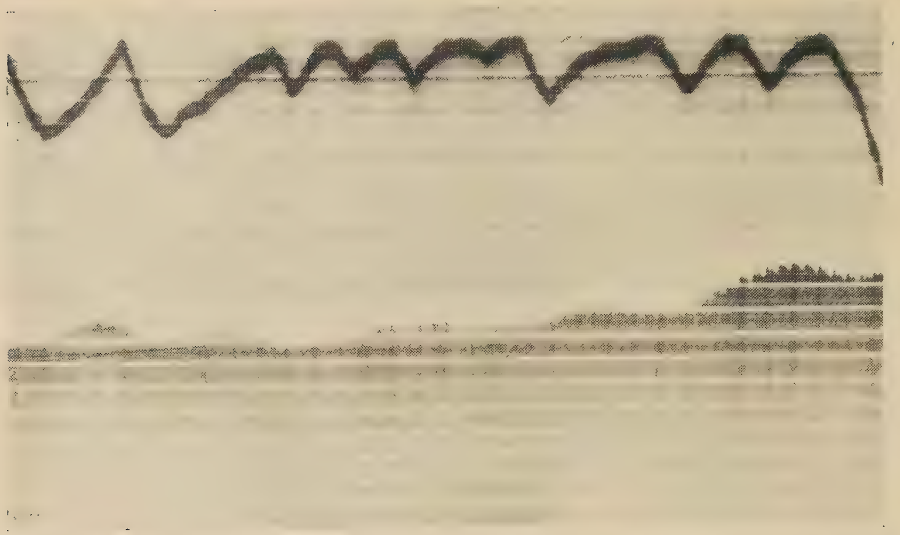


FIG. 1 (*a*).—Respiratory tracing and plethysmogram of a hyperventilator. This is the "normal" breathing pattern of this patient. Notice the gross irregularity including involuntary deep breaths. Also note the small pulse volume.

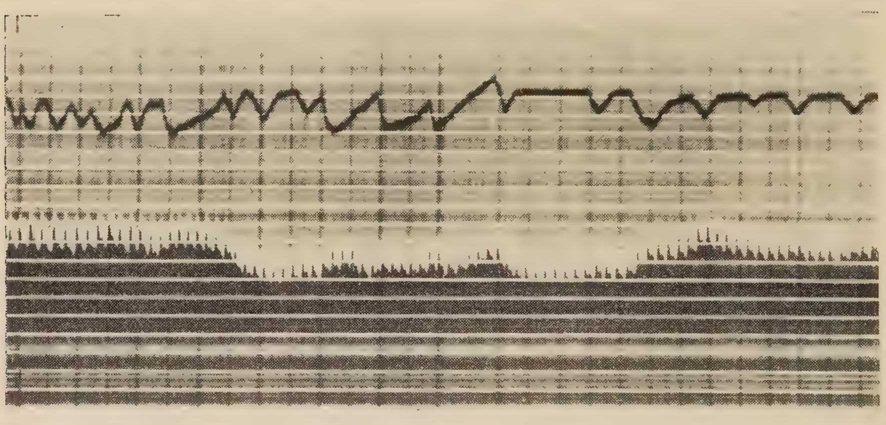


FIG. 1 (*b*).—Respiratory tracing and plethysmogram of a normal subject when emotionally disturbed. Note that an irregularity of breathing similar to that shown in Fig. 1(*a*) is present.

*Pathogenesis*

Within a few seconds of overbreathing the alveolar $CO_2$ tension drops from the normal of 40 mm. Hg to 15–20 mm. Hg. It does not diminish much further despite continued overbreathing. The resulting alkalaemia is responsible for many of the clinical manifestations.

## CEREBRAL SYMPTOMS AND SIGNS

### *Symptoms*

Thirty-one patients complained of some cerebral disturbance. Twenty-six of them described it as one of several complaints. Where peripheral complaints were prominent, cerebral complaints received cursory mention. The most common complaint was giddiness, faintness or lightheadness—never a true vertigo. This sensation was always aggravated by the upright posture and relieved by recumbency. It was often accompanied by blurring of vision or "black spots before the eyes". Patients were usually afraid of falling and were unsteady on their feet: one man seldom ventured out of his house because, if he had to cross a busy street, his "hands and feet would tingle and he would become so giddy that he was afraid he would fall"; one woman refused to climb stairs because of her lightheadness. "A tight band round the head", or actual headache, was sometimes complained of. Some patients said they felt as if they were drunk and staggered and one woman who had a hyperventilation attack on a bus was actually threatened by the conductor with a charge of drunkenness.

Several patients complained of "a feeling of unreality" as though they were not quite in touch with their surroundings. A doctor once described to me a seance which he attended in company with a young girl who had recently been bereaved. He said: "In the darkness I could hear her breathing heavily. Suddenly she screamed and as the lights were switched on and a pencil thrust into her hand she scrawled DAD with tetanic fingers. The girl, because of the strange feeling of unreality, was quite sure she had been in touch with the spirit of her dead father."

Drowsiness—often associated with yawning—was often seen after a hyperventilation test of 2–3 minutes. One woman always hyperventilated herself to sleep.

Loss of inhibition is common. Several patients wept or laughed during attacks. For this reason a hyperventilation test can sometimes be used as a simple abreaction technique.

One patient presented with abnormal behaviour as her chief complaint. Her story was that she had been worried for some months about her chest. One morning she had to run to catch a train. She was breathless as she got in and became alarmed at her "bad chest". For the next 20 minutes she sat in the train with a feeling of "not being able to get a deep enough breath". As the train drew into the station she felt so peculiar that, hardly knowing what she was doing, she wrenched open the door of the moving train and fell heavily on to the platform. A hyperventilation test reproduced this "peculiar feeling" so exactly that she attempted to get up and run out of the room.

The term "blackout" was not infrequently used by patients. This almost always turned out to be a sense of giddiness with a fear of falling but no actual loss of consciousness. Only five patients in this series had a disturbance of consciousness gross enough to merit the term "blackout". (See Appendix—cases 14, 16, 17, 24, 26.)

It is interesting that of the nine patients who had no cerebral symptoms six always had their hyperventilation attacks when in bed. The recumbent posture diminished cerebral symptoms.

### *Signs*

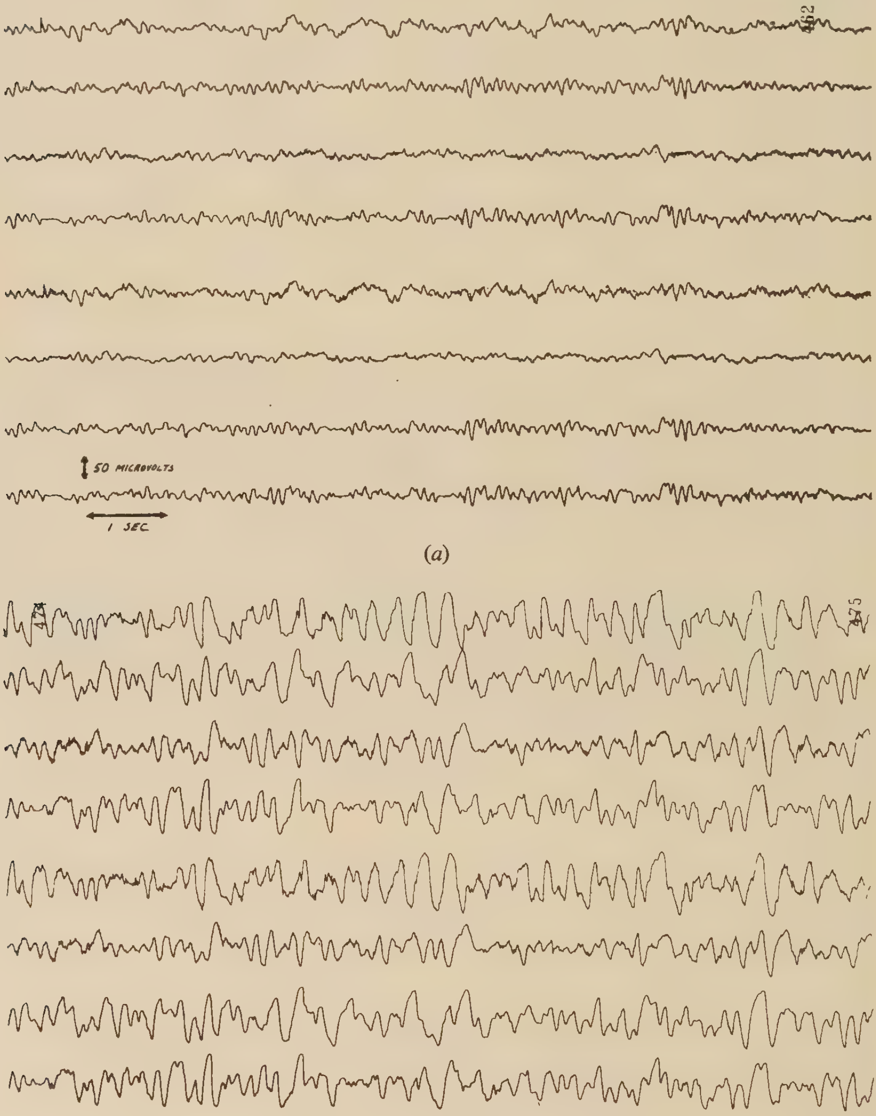
The disturbance of consciousness can be well illustrated by getting the patient to do a task involving a fair degree of co-ordination, or to solve an arithmetical problem, immediately after several minutes of overbreathing.

### *Pathogenesis of the Cerebral Symptoms*

The cerebral symptoms point to some definite but easily reversible change in brain activity. This is supported by the fact that there is usually a correlation between disturbance of consciousness and electroencephalographic changes during hyperventilation. Certain of these changes are regarded as indicative of epilepsy.

Four types of EEG change may occur:

1. The most common is the appearance of a high-voltage slow rhythm of 2 to 3 cycles per second—the so-called delta rhythm. (See Fig. 2.) The factors which determine the appearance of delta activity are not completely understood. Brazier, Finesinger and Schwab (1944) working with young adults, found that 38 per cent. of "normals" developed delta activity in the third minute of hyperventilation, so that there is an individual susceptibility. Other



(a)

(b)

FIG. 2.—Electroencephalogram of a subject: (a) before 2 minutes hyperventilation; (b) after 2 minutes hyperventilation. Note the appearance of large delta waves in (b).

factors which favour the development of delta activity are youth, the upright posture and a low blood-sugar level. Brazier claimed that if the blood-sugar level was lowered by insulin all normals developed delta activity. All workers agree that delta activity results ultimately from acapnia but they do not agree about the immediate cause. Three possibilities have been suggested (Hill and Parr, 1950).

(*a*) Inadequate compensatory vasoconstriction (Gibbs, Lennox and Nims, 1942).

(*b*) Cerebral anaemia due to vasoconstriction resulting in anoxia and glucose deprivation (Davis and Wallace, 1942).

(*c*) Reduction in the activity of the cholinergic supply to the blood vessels of the cortex resulting in excessive local constriction (Darrow and Pathman, 1943–44).

It has been suggested that a reasonable working hypothesis is "to regard the delta activity as resulting from a failure of oxidative metabolism in the brain cells and in particular of the oxidation of glucose since the instability may often be prevented by raising the $O_2$ and glucose levels in the blood". (Hill and Parr, 1950.)

It is not unusual, however, for delta activity to appear with no clearly detectable change in consciousness and apparently some subjects can become unconscious during hyperventilation and yet show no delta activity.

2. The resting alpha rhythm may increase in amplitude without becoming faster than the normal 8–14 cycles per second.

3. Abnormally fast rhythms may appear or fast rhythms already present may increase in amplitude. If an already existing fast rhythm doubles in voltage, or a fast rhythm appears, especially if it appears in bursts, the present tendency is to classify the phenomenon as epileptic.

4. Both fast and slow rhythms may appear in the well-known spike and wave pattern. This is almost certainly diagnostic of epilepsy. It usually occurs in young patients with petit mal.

These EEG changes disappear within a few seconds when the subject stops overbreathing. It seems that the loss of $CO_2$ is the fundamental factor. The cerebral circulation is very sensitive to chemical changes in the blood and it is generally accepted that the fall in the $CO_2$ content of the blood as a result of overbreathing causes the cerebral blood vessels to constrict, thus both reducing the blood flow and conserving $CO_2$ in the brain. Kety and Schmidt (1946), using the nitrous oxide method, measured changes in cerebral blood flow in five volunteers during active and passive hyperventilation. They found that cerebral blood flow invariably diminished—the mean decrease being 33 per cent. during active hyperventilation and 35 per cent. during passive hyperventilation. The cerebral arteriovenous $O_2$ difference invariably increased (average 58 per cent.) and the cerebral $O_2$ consumption showed a consistent and significant increase during active hyperventilation (average 15 per cent.) but no change during passive hyperventilation.

## PERIPHERAL NEUROLOGICAL SYMPTOMS AND SIGNS

Thirty-three patients complained of these.

(a) *Sensory* symptoms occur earlier than motor. They appear at a variable time after the onset of overbreathing, depending on the rate and depth of breathing and the susceptibility of the subject. Some patients have marked symptoms after two or three deep breaths and others may overbreathe for 5 or more minutes before getting symptoms. The symptoms consist of paraesthesiae variously described as "tingling", "pins and needles", "electric shock", "deadness" or "numbness". They always start distally. The usual pattern of spread is first in the finger tips and very often first in the ulnar area; then in the toes and finally in the peri-oral area and tip of the nose. Any one of these sites may be first or solely involved, depending on individual susceptibility. One extremity is frequently involved before the other and it is not necessarily the dominant one; one woman always got her paraesthesiae in the left hand and around the left side of her face and left ear. She said that her left ear also got deaf during attacks. She was quite sure that this was a form of "stroke". She was right-handed.

Finally, there may be a generalized tingling. Two patients complained that their teeth were tingling.

A feeling of spasm or tightness in the muscles of the extremities or midline structures, such as the epigastrium or sternum, is a common complaint.

Objective sensory loss then develops in the affected areas. Touch and later pain sensation is interfered with.

(b) *Motor* manifestations consist of fascicular twitching which first involves the face and small muscles of the hands. It may appear spontaneously or be elicited by tapping near a peripheral nerve (Chvostek's sign). Actual tetanic spasm was complained of by six patients—two of whom were alkalotic because of vomiting. If hyperventilation is continued the characteristic spasm of hands and feet develops. In the hand this consists of adduction and extension of the thumb with extension of the interphalangeal and flexion of the metacarpophalangeal joints. Finally flexion of the wrist occurs. In the feet the ankles are inverted, tarsus flexed and toes extended. In the face the eyes have a staring look due to contraction of the orbicularis oculi, the jaw is clenched and the corners of the mouth drawn up.

Patients often complain of difficulty in articulation because of "stiffness" of the mouth. The larynx may be involved with the production of stridor.

One patient complained of laryngeal stridor, which is uncommon in adults. She was a European female of 52 years who said that four years previously she had had a thyroidectomy. At this operation her recurrent laryngeal nerve was cut. One month after the operation she was recognized as being myxoedematous. Eight months after the operation she had an attack of stridor. After this she often wakened herself and her family at night by stridor. Her serum calcium was normal. During the day she sometimes got a tingling in her hand and a feeling of "not being able to get a deep enough breath".

Spasm of hands and feet may be painful. It can be relaxed voluntarily, despite continued hyperventilation, if the spasm is not too well established. In one subject who demonstrated this, there was a lag of a few seconds before the hand reverted to its tetanic posture.

Proximal muscles are later involved and if the spread of the spasm is mainly unilateral there may be some diagnostic difficulty: one woman always got tingling in the left hand with drawing up of the left shoulder; the possibility of a Jacksonian attack was considered in her case but the whole picture was reproduced many times by hyperventilation tests.

Muscles of trunk and head are later involved with the development of opisthotonus. Three cases (not included in this series) were sent to hospital diagnosed as meningitis because of this marked opisthotonus and neck rigidity. Within a few minutes of cessation of overbreathing the neck rigidity disappeared and the head assumed its normal position.

Involvement of trunk muscles may be associated with abdominal pain and rigidity. This presented a diagnostic puzzle in two surgical cases. They were both patients with partial intestinal obstruction who had been vomiting and so were in a state of alkalosis. They became alarmed about themselves and began to overbreathe. Tetanic spasm developed and later rigidity of abdominal muscles. The question of perforation then arose but once they had stopped overbreathing the rigidity disappeared.

Marked muscle tenderness may be present in limbs previously the site of tetanic spasm. A nurse was sitting talking to her friends when she developed tingling in hands and feet. She then collapsed with tetanic spasms in the extremities. After a night of hyperventilation tetany her muscles were so tender and "weak" that she was sent into hospital as a case of poliomyelitis.

Hemi-tetany is very uncommon. Patients often start with paraesthesiae in one limb but by the time tetanic spasm has supervened they have generalized symptoms and signs. If, however, there has been some organic nervous disease, especially hemiplegia, hyperventilation may result in hemi-tetany. One such case was a European male of 38 years who one month before admission to hospital had developed a left-sided hemiplegia due possibly to a vascular accident. His signs cleared up so that clinically there was only minimal evidence of a hemiplegia. One morning he woke with his left hand in tetanic spasm. Then he became conscious of a tingling feeling on the left side of his mouth and his left leg became stiff. "I did not think I was overbreathing but my wife says I was breathing deeply." The attack passed off in 15 minutes and he had many such attacks before admission to hospital. A hyperventilation test was carried on for 30 minutes. He developed well-marked tetany on the left side with minimal paraesthesiae on the right. Plethysmography showed no difference in the pulses on the left and right sides.

### *Pathogenesis*

Kugelberg (1946 and 1948) claimed that tetanic activation was ultimately dependent on peripheral nerve change. The pattern of spread was always the same in that the long tactile fibres to face and hands were first activated, which caused the sensation of tingling. Later other afferents were activated—giving rise to the sensation of spasm. Then the longest motor fibres to the small muscles of the hand were excited (extensors having a lower threshold than flexors). Finally the shorter fibres to flexor carpi ulnaris were affected.

Kugelberg has done electromyographic studies to show not only the same distinctive type of response but also a distinctive spread of response in all varieties of tetany. He emphasized the primary involvement of the nerves to face and hands and pointed out that these were the parts best represented in the cerebral cortex and most recent phylogenetically. He suggested that the difference in vulnerability of the various nerve fibres might be due to the size of the fibre or to the state of calcium in the fibre.

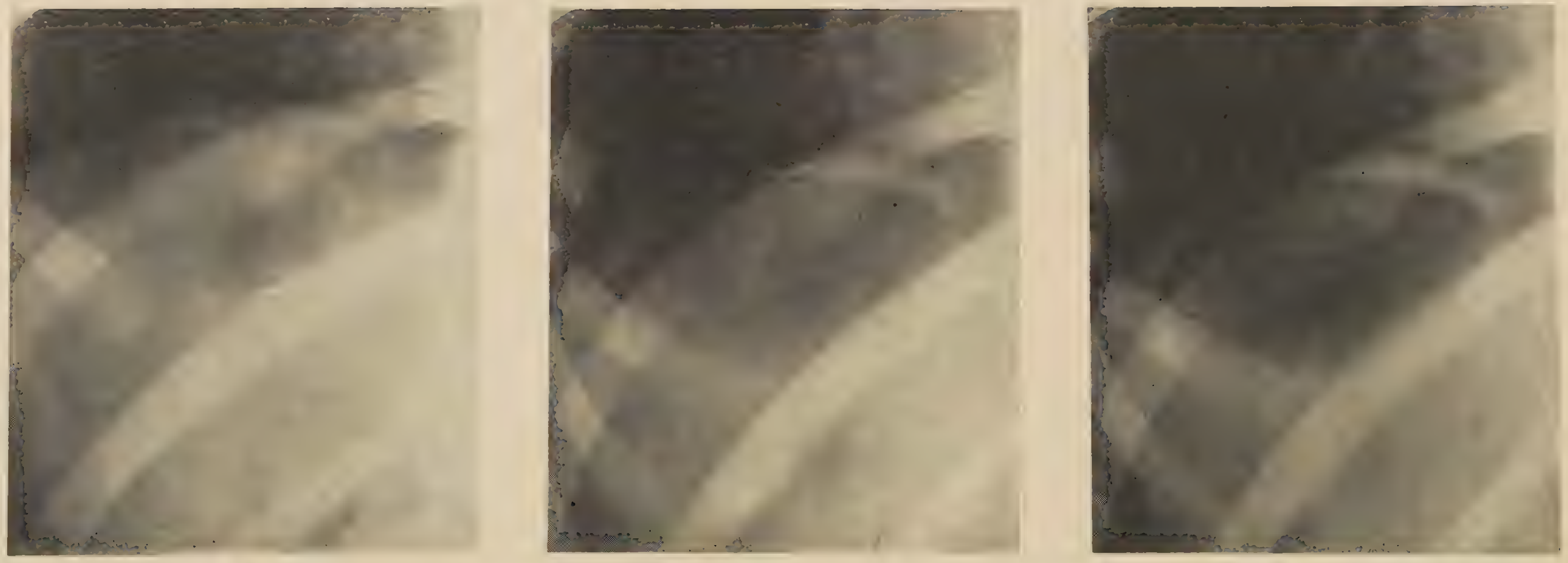
## Alimentary Symptoms and Signs

### *Symptoms*

Many patients complained of dryness of the mouth which was probably due to overbreathing through the mouth.

One patient complained of a bitter taste in the mouth; another of a fishy taste.

Eight patients complained of abdominal distension during an attack. This was usually relieved by belching.



(*a*) (*b*) (*c*)

FIG. 3.—X-ray of the stomach (*a*) before, (*b*) Immediately after, and (*c*) 10 minutes after 5 minutes overbreathing in a normal subject. Note the increase in amount of intragastric air after overbreathing. The time of exposure and development was constant for all three X-rays.

Two patients complained of epigastric discomfort. One of them said, "During the attack my stomach feels as though it has turned to jelly." Another complained of a "vice-like" feeling across the epigastrium.

One patient in this series complained of nausea, and it was complained of by one normal control after a 2-minute overbreathing test.

### *Signs*

Rigidity of abdominal muscles may be striking during an attack of hyperventilation tetany.

### *Pathogenesis*

Air swallowing has been suggested as one possible machanism for the distension. (See Fig. 3.)

Another explanation for apparent gross distension is a marked increase in lumbar lordosis (Westdahl, 1951; Roussak, 1951). This was seen in a Malay woman who always became drastically "distended" during hyperventilation. Her back was found to be arched several inches off the couch and she refused to relax it saying that it would aggravate her breathing difficulty if she did so.

A tight feeling and rigidity of abdominal muscles is due to increased neuro-muscular excitability.

## SYSTEMIC CIRCULATORY SYMPTOMS AND SIGNS

### *Symptoms*

Eight patients complained of praecordial pain. In one case the pain had all the characteristics of angina but was apparently never provoked by any form of exercise other than hyperventilation. One woman got a "burning" feeling under the sternum after a few minutes of overbreathing. Another patient complained of "a sharp pain under the breast bone which shoots up to my left shoulder and round my neck". Two patients complained of an oppressive feeling in the left praecordium "as though something is pressing on my heart". Another patient complained of a "dull ache" over the left praecordium. Two patients said they got a sharp stabbing pain "like a knife" in the left mammary region.

Ten patients complained of palpitations. In one case it was the sole complaint.

Six patients complained of cold hands and feet, but in only one was it the main complaint. Several patients, after several minutes of overbreathing, complained of a generalized coldness and shivered violently.

Peripheral vasoconstriction was a striking feature in all cases after a few minutes of overbreathing. The hands and feet became cold and sweated freely. Two cases became cyanosed. In some cases the radial pulse was obliterated. An increase in pulse rate from 6 to 30 beats per minute occurred in all cases after a few minutes of overbreathing. (See experimental section.)

### *Pathogenesis*

Praecordial pain of the knife-like or aching left mammary variety might result from misuse of the respiratory musculature. Any departure from the normal smooth action of breathing might cause fatigue of intercostal muscles or of the diaphragm. Wood (1941) invoked diaphragmatic spasm as a cause of the praecordial pain seen in Da Costa's syndromes.

The "pressing pain round the heart" was relieved in both cases by belching, so that distension of the stomach caused by air swallowing might account for this form of discomfort.

Cardiospasm was thought to be responsible for praecordial pain in two cases.

Pain that simulates coronary artery disease has lead to serious diagnostic errors. Electrocardiographic changes also occur during overbreathing so that the problem may become very difficult. The changes consist of lowering of the S–T segment and lowering or inversion of T waves. There are various theories to account for these changes. Some workers invoke anoxia of heart muscle or coronary vasoconstriction. Others put them down to changes in the position of the heart or associate them with the tachycardia that occurs.

It can be argued that overbreathing is a form of exercise so that a true angina could be precipitated by a hyperventilation test. It is also true that some patients with undoubted coronary artery disease hyperventilate through fear and anxiety. Several patients (outside the present series) with definite evidence of coronary occlusion described paraesthesiae in the limbs as part of the attack. In these cases careful history taking revealed that the patients had been overbreathing.

Tachycardia is partly explained by the muscular exercise of overbreathing.

The peripheral vasoconstriction that occurs in hyperventilation is dealt with in the experimental section.

### URINARY SYMPTOMS AND SIGNS

Urinary changes which have been reported after overbreathing are alkalinity of the urine, the presence of bicarbonate but little or no ammonia, diuresis and slight ketonuria.

In this series two patients complained of a diuresis after overbreathing. In six normal controls the urine became alkaline and showed an increase in phosphates after 8–10 minutes of overbreathing.

#### *Pathogenesis*

Some of the urinary changes result from the alkalosis. It is possible that the diminution in cerebral blood flow may partly account for the diuresis or the phosphaturia through a pituitary or hypothalamic mechanism.

The phosphaturia is interesting because, according to Brown and Hilton (1930), it is "noted most frequently in association with wasting, worry, serious mental depression or severe mental work or strain".

### GENERAL SYMPTOMS AND SIGNS

Fatigue is a common complaint after a hyperventilation test.

#### *Pathogenesis*

Hyperventilation is a vigorous form of physical exercise.

### COMMENT ON CLINICAL EFFECTS OF HYPERVENTILATION

It is characteristic of the hyperventilation syndrome that, in spite of its wide and varying pattern of symptoms and signs, the nervous system is always involved. Every case in this series had some evidence of neurogenic dysfunction. Engel, Ferris and Logan (1947) suggested that patients could be classified according to whether this neurogenic dysfunction was mainly cerebral or mainly peripheral. A grouping of the patients in the present series in this way gives: Mainly cerebral involvement, seven cases; mainly peripheral neurological involvement, nine cases; both cerebral and peripheral, twenty-four cases.

Individual patterns of reaction tend to remain stable in different subjects: a subject whose first symptom is a tingling in the left ulnar region will always tend to start with that symptom.

The pattern is, however, sometimes upset. Among the factors which seem to disturb it are:

(*a*) Posture. The upright posture aggravates cerebral symptoms.

(*b*) Low blood-sugar level. This also aggravates cerebral symptoms. Engel *et al.* (1947) quoted a case of a woman who always reacted to overbreathing with cerebral symptoms if she was starving and with tetany if she had just had a high carbohydrate meal.

(*c*) Unknown factors. A few subjects vary in their reaction patterns for no apparent reason. A medical man who often acted as a subject in these experiments would on one day manifest tetanic spasm, on another cerebral symptoms and yet on other occasions laryngeal stridor would be an early and striking manifestation.

The time of onset and the severity of symptoms and signs vary both from subject to subject and at different times in the same subject. Some subjects get severe symptoms so quickly after starting to hyperventilate that as a clinical observation they can be classed as hypersensitive. There is at present, however, no satisfactory scientific measure of this hypersensitivity. O'Donovan (1943) defined a hypersensitive person as one who developed tetany within 2 minutes of overbreathing at the rate of 55–60 breaths per minute, or who was so incapacitated by the severity of the symptoms that hyperventilation could not be carried on for longer than 2 minutes. This does not take into account depth of breathing, or the fact that subjects with a large vital capacity may blow off their $CO_2$ more rapidly. It also ignores the subjective factor that a person who is tired or feeling demoralized may very quickly feel that his symptoms are too severe to enable him to carry on. Many patients in this series—where the breathing rate used was 40 breaths per minute—complained that "they could not carry on" when asked to overbreathe for 2 or 3 minutes. Some refused to continue for more than a few seconds. Yet they could not be called hypersensitive to overbreathing in any measurable physiological sense.

Individual sensitivity does not necessarily make one a sufferer from the hyperventilation syndrome, though one is more likely to develop dramatic symptoms if one does overbreathe. Only three subjects, using tetany production within 2–3 minutes of overbreathing at the rate of 40 breaths per minute as the criterion for hypersensitivity, could be classed as abnormally sensitive. Two of these were not patients but "normal controls".

Variation in the time of onset and the severity of symptoms in the same subject at different times seemed to be due to fatigue or stress, or both. Patients often remarked that although the symptoms produced in a hyperventilation test were essentially the same as those produced during involuntary overbreathing in response to stress, they were less severe. The physiological and biochemical changes produced in the body during stress lie outside the scope of this thesis. Mention must be made, however, of one factor which may play a part in enhancing the effect of symptoms directly attributable to overbreathing. This factor is that of adrenaline release. Adrenaline is a well-recognized respiratory stimulant; it may be involved in initiating or sustaining the overbreathing. Further, by its action in causing vasoconstriction of skin vessels, adrenaline enhances the reflex peripheral vasoconstriction of overbreathing. The effect of adrenaline in precipitating tetany in subjects rendered alkalotic by overbreathing has been sporadically investigated for many years. In 1926 Duzar and Hensch claimed that if normal children overbreathed for 5 or 6 minutes they could be made actively tetanic by intravenous adrenaline, without further hyperpnoea. McCance (1932) thought that the only effect of adrenaline administration in aggravating hyperventilation tetany was its action as a respiratory stimulant. Harvey and Lilienthal (1942) found that intra-arterial injection of adrenaline in hypocalcaemic patients precipitated tetanic spasm. They thought that this was due to the "abrupt distortion of the potassium-calcium ratio" which occurs after adrenaline administration and not to the intense vasospasm that also occurred, or to any change in breathing rate. They investigated one subject suffering from the hyperventilation syndrome and reported that adrenaline, without preliminary hyperpnoea, did not precipitate tetanic spasm. But their final comment on this case appears significant: "after the test he began moderate, voluntary hyperventilation and induced well-marked carpopedal and facial tetany within one minute".

## Diagnosis and Differential Diagnosis

Diagnosis is not difficult if one is aware of the syndrome. It must be made on positive grounds with a clear knowledge of the pathogenesis. If a good history is taken the majority of cases give a story of periodic attacks of both peripheral and central nervous system disturbances. Such a story, in the absence of any signs of organic nervous disease, suggests the hyperventilation syndrome. If, in addition, there is respiratory distress unrelated to exertion, the diagnosis is certain. If a case presents with cerebral symptoms alone, or with some other effect of overbreathing, such as tachycardia, the diagnosis may become more difficult. If careful attention is paid to all symptoms, however, and not only to the one which has made the deepest impression on the patient, it is usually possible to elicit the characteristic story of respiratory difficulty associated with paraesthesiae and giddiness. It must be remembered that patients seldom mention any respiratory difficulty because they are not aware of its relevance. In these cases leading questions are probably justified and the report of relatives may prove helpful.

Finally, a hyperventilation test will clinch the diagnosis. The patient is instructed to overbreathe for several minutes at the rate of 30 or 40 breaths per minute. In this series most patients reproduced, in 1 to 3 minutes, the symptoms of which they had complained. Some took as long as 8 to 10 minutes. It is important to see that they are really overbreathing and to remember that the upright position is the best one for eliciting cerebral symptoms and the recumbent position the best for eliciting peripheral symptoms. The object of the test is to reproduce the patient's symptoms, so that the similarity between the symptoms and those produced by overbreathing is recognized. The time taken to develop the syndrome is not very important, except very broadly, because the depth and rate of breathing vary from patient to patient. A metronome is of help in regulating the rate. Patients also vary from time to time in their susceptibility to the test depending on their emotional state, blood-sugar level, etc.

The following are some of the vague or erroneous diagnoses with which these patients presented themselves:

### 1. *Neurosis or "Functional Disease"*

Fifteen patients were thus diagnosed. In other words their illness was recognized as being of emotional origin, but no further classification was attempted. There can be no real understanding by the doctor or the patient of an illness vaguely labelled "neurosis". If the patient is getting symptoms as real as paraesthesiae or tetanic spasm his physiology is disturbed. Hyperventilation is one of the mechanisms by which this disordered physical state is brought about.

### 2. *Epilepsy*

Three cases were thought to be epileptic. The diagnosis was made on a story of sudden loss of consciousness. A careful history showed, however, that all these cases had premonitory signs of respiratory distress. If an attack is witnessed by a doctor the differentiation from an epileptic seizure is easy. In the tetanic "fit" the striking thing is the increased rate and depth of breathing. A general stiffening of the body occurs—opisthotonus is marked—but no motor jerking. Occasionally the posture of the hands is unmistakably tetanic. Consciousness is seldom completely lost though the patient may not respond to pin-prick for a few seconds. Tongue biting and incontinence seldom occur. Cyanosis is relatively uncommon though it may occur if overbreathing is followed by a long period of apnoea. Many people imagine that grand mal seizures are readily precipitated by overbreathing. Most authorities say it is very uncommon to induce a grand mal seizure in this way, though petit mal attacks are readily so induced. Gibbs, Lennox and Gibbs (1940) claim that patients with petit mal have a low $CO_2$ level in the blood and so are unusually susceptible to any loss of it through overbreathing.

### 3. *Hypoglycaemia*

Three patients were thought to be suffering from hypoglycaemic attacks. There are several points of similarity: the periodic nature of the attacks, the excessive sweating and confusion. However, respiration remains unaffected in hypoglycaemia until the patient is deeply comatose and many transient attacks of hypoglycaemia are uncommon without some obvious organic disease becoming manifest. One diabetic who was hypoglycaemic through insulin over-dosage was referred as a case of the hyperventilation syndrome.

### 4. *Thyrotoxicosis*

The diagnosis of thyrotoxicosis is always difficult and the physical similarity between an anxious and a thyrotoxic patient is well-known. Here again the respiratory difficulty and the reproduction of symptoms and signs by a hyperventilation test are valuable. Two cases in this series were thought to be thyrotoxic.

### 5. *Peripheral Vascular Disease*

Many doctors who are aware of the hyperventilation syndrome do not realize that one of its manifestations is a striking peripheral vasoconstriction which, because of its periodic nature, may be confused with Raynaud's disease. The relationship to cold is absent, however, and the other manifestations of the hyperventilation syndrome should help to differentiate the two conditions.

### 6. *Poliomyelitis*

One case was admitted to an infectious diseases hospital with this diagnosis because of residual muscle tenderness and a feeling of "lameness" in the legs after a night of overbreathing.

### 7. *Organic Cardiac Disease*

Almost half the patients in this series thought they had heart disease. In some cases this belief had received support from their doctors. The error on the part of the doctor was usually made because of lack of careful history taking, a fear of missing something organic, and ignorance of the ECG changes that occur with overbreathing. It is a serious error in an already anxious patient. Two patients had spent 6 weeks in bed—diagnosed as cases of coronary thrombosis. Both these patients described a very severe substernal pain and belching with the attack. They had probably been swallowing air and had developed an associated cardiospasm.

### 8. *Da Costa's Syndrome*

Attempts to explain the symptoms of this syndrome by hyperventilation have been made for a long time. White and Hahn (1929) found that 80 of 100 patients with this syndrome had sighing dyspnoea, whereas only 76 of 400 normal controls showed sighing dyspnoea. They concluded that hyperventilation probably accounted for many of the symptoms of Da Costa's syndrome.

Wood (1941) also investigated the problem and concluded that hyperventilation was unimportant in this syndrome. He thought, however, that the left mammary pain common in Da Costa's syndrome might be caused by a habit of breathing intercostally with neglect of the diaphragm and resultant diaphragmatic spasm. There may be an overlap here with the hyperventilation syndrome as left mammary pain is not uncommon.

In 1938 Soley and Shock investigated seven patients in detail and concluded that "the respiratory alkalosis resulting from hyperventilation produces the symptoms of effort syndrome".

In 1945 Friedman said "although hyperventilation may occasionally be found in patients with neuro-circulatory asthenia, it is not an initial aetiological factor of any real importance in the production of the symptoms from which they suffer".

Although there may be some overlap between these two conditions, the dyspnoea in Da Costa's is characteristically related to exertion, and neurogenic dysfunction which is so striking in the hyperventilation syndrome is absent.

### 9. *Tetany*

Tetanic spasm is not a common feature of the hyperventilation syndrome. It occurred in six patients in this series and two of these patients were alkalotic through vomiting before they hyperventilated. Confusion with other varieties of tetany is unlikely. If difficulty does arise the normal serum calcium level will rule out hypocalcaemia and the history will rule out alkalosis from ingestion of alkali or from excessive vomiting.

### 10. *Acroparaesthesiae*

This condition has in common with the hyperventilation syndrome periodic attacks of paraesthesiae in the fingers with no signs of organic nervous disease. Its symptoms, however, are related to posture, not to breathing, and are more often nocturnal. The patient with acroparaesthesiae often complains of a "bloated" feeling or actual swelling of the fingers. Only one hyperventilation patient (outside this series) complained of swelling of the hand during an attack.

## TREATMENT

1. Much of the treatment is built around the hyperventilation test already described, which is not only diagnostic, but for the following reasons, of immense therapeutic importance:

(*a*) The majority of patients think that their symptoms are due to some serious organic disease. The reproduction of these symptoms by overbreathing does more than any words can do to assure them that either no serious organic disease is present, or, if such disease is present, it is not the cause of the symptoms and should be dealt with as a separate problem. A not uncommon example of the co-existence of the syndrome with organic disease is the patient who has had a cardiac infarction and has become anxious about his heart. The anxiety results in hyperventilation which causes distressing symptoms. The patient automatically assumes that these symptoms indicate that his heart condition is worse.

(*b*) During the test the patient is shown how much more difficult it is to hyperventilate through the nose and the value of nasal breathing in preventing hyperventilation is emphasized. Air swallowing is impossible with nasal breathing.

(*c*) Some observers, impressed by the predominantly intercostal character of these patients' breathing, stress the importance of teaching them to breathe abdominally.

(*d*) A demonstration of the relief gained from symptoms by breath-holding or by re-breathing into a paper bag or hat, etc., is an essential part of the test. Breath-holding is ideal, because it not only relieves the symptoms which result from loss of $CO_2$, but also relieves symptoms such as peripheral vasoconstriction, tachycardia, etc., which result from the mechanical act of overbreathing. Many patients, however, find it impossible to hold the breath because the sensation of "not getting enough air into the chest" is so over-powering. If they re-breathe into a bag or hat the relief of the alkalotic symptoms usually eventually stops the hyperventilation.

2. Medication is usually not necessary apart from sedation in anxious patients. For this purpose phenobarbitone $\frac{1}{2}$–1 grain three times a day and sodium amytal 1–3 grains at night, is useful.

3. Calcium is of doubtful value. Many patients have been given calcium gluconate intravenously by their doctors during attacks of hyperventilation tetany and said that it relieved their symptoms. It is possible that the mere fact of calling in a doctor who embarked on active treatment was so reassuring that they stopped overbreathing. It is not justifiable to keep a patient on regular calcium or vitamin D medication. O'Donovan's claim that such therapy abolishes hypersensitivity to the effects of overbreathing is an isolated report and the therapy is not without danger.

4. Kerr, Gliebe, Soley and Shock (1939) found ammonium chloride of value in "acidifying" their patients so that it became more difficult for them to become alkalotic if they did overbreathe.

5. The emotional stress which has caused the hyperventilation usually needs to be treated. The association between breathing disorder and stress is explained to the patient and he is given the opportunity to discuss his emotional problems. Occasionally this happens quite spontaneously immediately after a hyperventilation test because of loss of cortical inhibition.

No attempt was made to do any extensive psychoanalysis on the patients in this series. Patients appeared to adjust themselves well if given an early opportunity to discuss their problems.

Psychotherapy is not always necessary. Some patients, once shown the technique for breaking the vicious circle of symptoms from which they are suffering, appear able to make a good general adjustment on their own.

6. The technique of progressive relaxation was taught to all patients who were very tense.

## EXPERIMENTAL INVESTIGATION OF THE PERIPHERAL VASCULAR PHENOMENA OF THE HYPERVENTILATION SYNDROME

### HISTORICAL REVIEW

It is more than 50 years since the association between deep breathing and peripheral vasoconstriction was first noted. Binet and Sollier (1895) were the first authors to mention that a diminution in finger volume occurred with deep breathing. In 1924 Uhlenbruck again mentioned this association.

In 1933 Goetz demonstrated that a single deep breath produced a profound peripheral constriction. Associated with this he recorded a decrease in skin temperature, a drop in the rate of blood flow and a slowing, and, in some cases, a stasis in capillary blood flow.

In 1935 Goetz made a detailed study of the effects of a single deep breath and concluded that the diminution in blood flow was reflex since it was abolished by sympathectomy. Peters (1939) thought that the afferent stimulus came from the lungs themselves.

In 1936 the first comprehensive description in English was written by Bolton, Carmichael and Sturup. They, like Goetz, thought that the diminution in finger volume was due to a reflex whose efferent path was the sympathetic and whose afferent stimulus probably resulted from expansion of the chest wall. They did not obtain vasoconstriction with purely abdominal breathing.

In 1939 Mulinos and Shulman, using several different methods, showed that a deep inspiration caused marked vasoconstriction of the arterioles of the forearm and hand. They observed a complete standstill of blood in the capillary tufts, persisting for 3 to 5 seconds, after a deep breath.

In 1948 Gilliat showed that the fall in systolic pressure which accompanies a deep breath was not responsible for the peripheral vasoconstriction. He then described the reflex vasoconstriction in detail—saying that a single deep breath caused a diminution in finger volume of the order of 0·5 to 1 per cent. while the volume of each pulse decreased to 50 per cent. or less of its former value. The latency of the response was about 3 seconds and the finger usually regained its previous volume of 60 seconds. The constriction also occurred with passive inflation of the chest and did not occur after obstructed inspiratory or expiratory efforts. He disagreed with Bolton *et al.* about the lack of response with abdominal breathing and claimed that vasoconstriction did occur with fast rates of abdominal breathing.

In a separate article in 1948 Gilliat attempted to define the exact afferent pathway of the reflex. After experimenting with paraplegics he concluded that the afferent pathway entered the spinal cord mainly in the upper thoracic region but the possibility that the "limits of entry are somewhat wider was not excluded".

The reflex peripheral vasoconstriction after a deep breath has been invoked to explain the peripheral vasoconstriction after a deep inhalation of an unlighted cigarette (Goetz, 1942) and has been used to test for any regeneration of sympathetic fibres after a sympathectomy.

### METHODS AND MATERIAL

The state of the peripheral circulation under various conditions of breathing was studied.

Digital and pulse volume were recorded by means of the optical digital plethysmograph described in detail by Goetz (1948). Briefly, the method consists in enclosing the finger or toe in a plethysmograph which is made air-tight by sealing it with vaseline. The plethysmograph is connected to a specially made pipette graduated in 100ths of a ml. A column of alcohol is run into the pipette and any change in digital and pulse volume is transmitted to this column. The movements of the meniscus of the column are projected on to the paper of a recording camera. The ·01 ml. graduations of the pipette appear as white lines in the plethysmogram and serve as calibration for volume changes.

A 2-second time marker facilitates the calculation of the pulse rate. The respiratory tracing is recorded simultaneously by placing a cylinder of corrugated rubber round the subject's chest. This is connected by tubing to an all metal pressure capsule, designed by Goetz, and any movement of the chest wall is reflected on the plethysmogram.

With this apparatus the following can be read from the plethysmogram:

1. The pulse volume and shape of the pulse wave.
2. The digital volume.
3. The pulse rate.
4. The depth, rate and regularity of respiration.

The venous congestion test was done on a finger using the method recommended by Goetz (1943). Briefly, the method consists of the sudden inflation to 50–60 mm. Hg of a cuff placed round the forearm. This amount of inflation is sufficient to impede the venous return without interfering with the arterial inflow. The venous bed of the finger is normally only partly filled and during the first few seconds of the test is able to take up the arterial input without resistance. Consequently the rate of increase in volume during this period is, graphically, practically a straight line and the rate of blood flow can be calculated from it.

The gas flow was from a cylinder to a reservoir bag, connected to a B.M.R. mouthpiece *viâ* a non-return expiratory valve mounted at the mouthpiece. A B.M.R. nose clip was used. Warming and moistening the gas was done by introducing a Wolff's bottle containing warm water into the circuit.

Eight members of the series were used. Many of the normal controls were colleagues. All these subjects were free of organic vascular disease and stable enough to co-operate in the experiments. Some subjects were used several times.

Three patients who had had operations for removal of sympathetic ganglia were used. One of these had had a complete sympathectomy for hypertension. The other two were young women with acrocyanosis who were tested at varying intervals after a two-stage sympathectomy of the upper limbs.

All subjects reclined on a specially made couch with limbs nearly horizontal. They were instructed to relax in this position in a quiet dim room for 30 minutes before experiments were begun. The posture of the patient is important as marked changes in pulse volume result from change in posture (Goetz and Ames, 1949; Goetz, 1950).

### *The Normal Plethysmogram*

While the experimental part of this thesis is concerned with the peripheral vasoconstriction caused by deep breathing, certain other facts relating to changes in the peripheral vascular system are mentioned here because they may be important in the interpretation of some of the results obtained.

1. In the normal subject, even at rest, digital and pulse volume may show a waxing and waning which coincides with the respiratory cycle. These changes are usually explained as a result of the proximity of the vasomotor and respiratory centres in the medulla (Fig. 4). The changes can be induced or accentuated in a normal subject by adding $CO_2$ to the mixture breathed (Fig. 10(*b*)).

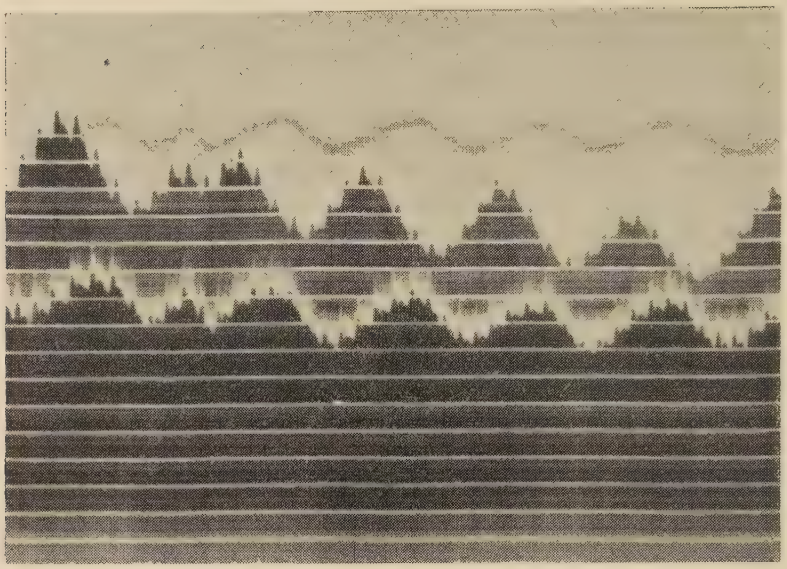


FIG. 4.—Plethysmogram of left index finger (upper tracing) and left big toe (lower tracing). Subject at rest. Note fluctuations in digital and pulse volume with respiration.

Goetz (1937) suggested that this did not result from the increased depth of respiration with $CO_2$ but that the $CO_2$ itself acted as a vasomotor stimulant.

2. In addition there are certain well-known extrinsic stimuli causing peripheral vasoconstriction. These are: mental activity; any sensory stimulus, e.g. pain; noise; a yawn; a sigh. Mental activity and a sensory stimulus produce a similar plethysmographic response. The peripheral vasoconstriction caused by them comes about independently of respiration. The degree and duration of the vasoconstriction are similar to that caused by a single deep breath (Figs. 5 and 6). A yawn and a sigh are in effect variants of a deep breath.

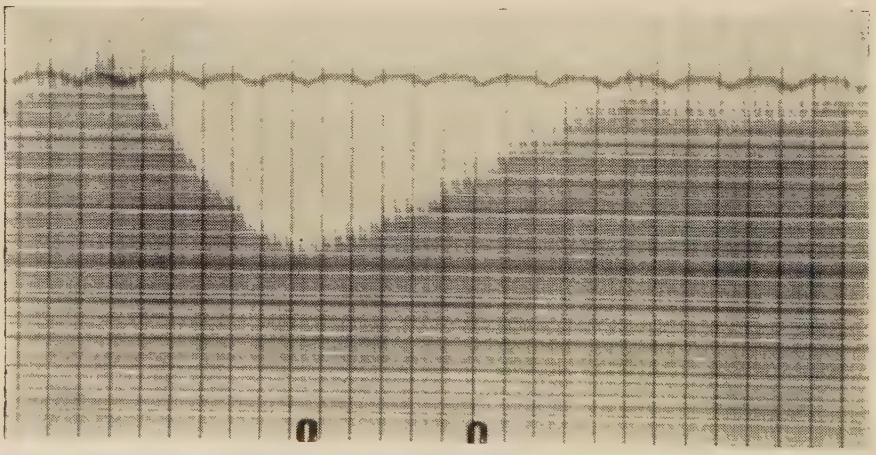


FIG. 5.—Plethysmogram of left index finger. Subject doing mental arithmetic. The period of calculation is indicated by the numbers.
Note the vasoconstriction which begins while the subject is being given the calculation.

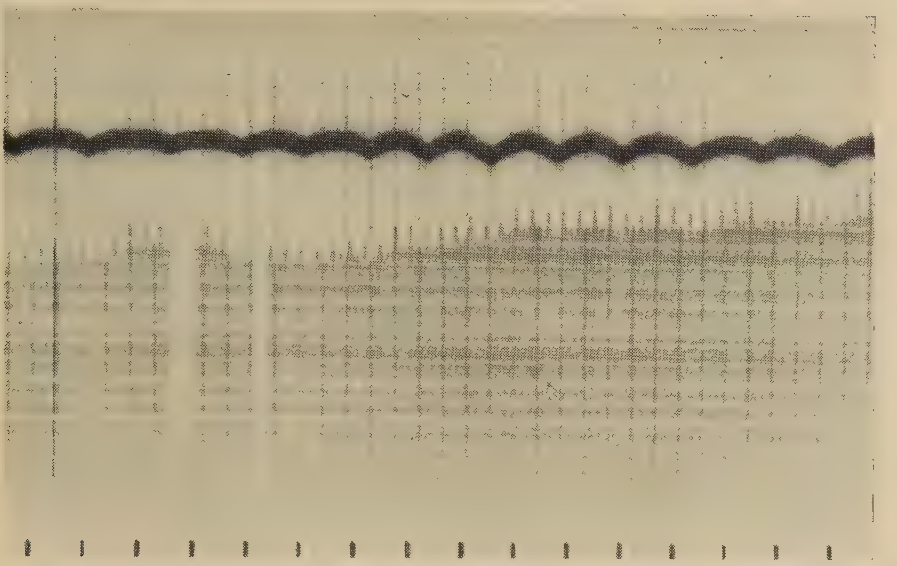


FIG. 6.—Plethysmogram of right index finger. Sudden noise made by dropping a basin. Duration of the noise indicated by vertical white lines. Note the vasoconstriction.

## INVESTIGATIONS

Three aspects of the peripheral vasoconstriction associated with breathing were investigated.

1. The effect of variations in a single breath.
2. The effect of 2 minutes of overbreathing.
3. The effect of overbreathing:
   (*a*) in ten subjects with one hand cooled and the other warmed.
   (*b*) in ten subjects with elevated limbs.
   (*c*) in two subjects with acrocyanosis, at varying intervals after the upper limbs had been sympathectomized.
   (*d*) in a subject with total sympathectomy.

### 1. *The Effect of Variations in a Single Breath*

(*a*) The usual response to a single deep breath is a considerable reduction in pulse volume. This occurs about 3 seconds after inspiration has begun and appears to coincide with the climax of the inspiratory phase. It is maximal from the beginning and a return to the original pulse volume takes about 30 seconds (Fig. 7).

Vasomotor tone is normally higher in the legs than in the arms if the subject is standing or reclining. As the subjects were reclining during these experiments toes were recorded less frequently than fingers because their low initial pulse volume made some of the results difficult to interpret.

The fact that toes do also constrict rules out the possibility that the vasoconstriction is due to compression of arm arteries by the movement of the shoulder girdle that accompanies a deep breath (Fig. 8).

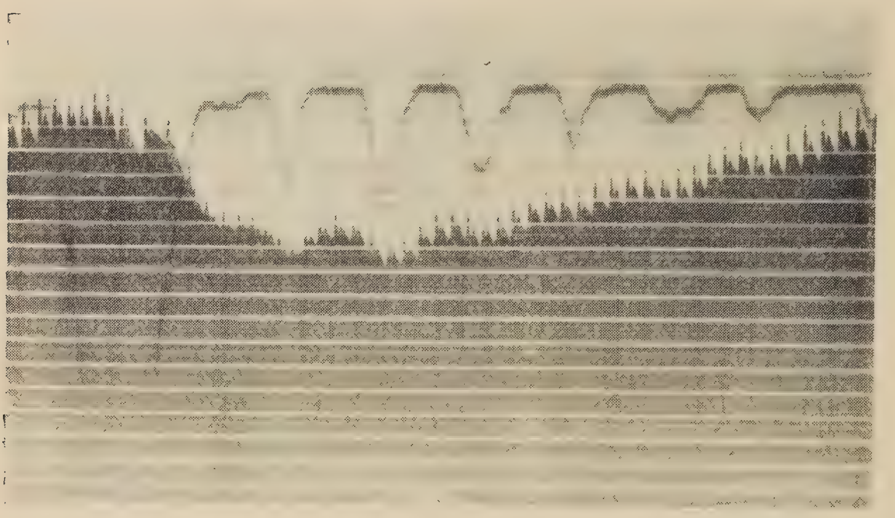


FIG. 7.—Plethysmogram of left index finger. Subject instructed to take one deep breath. Note vasoconstriction which takes a few seconds to occur and is considerable.

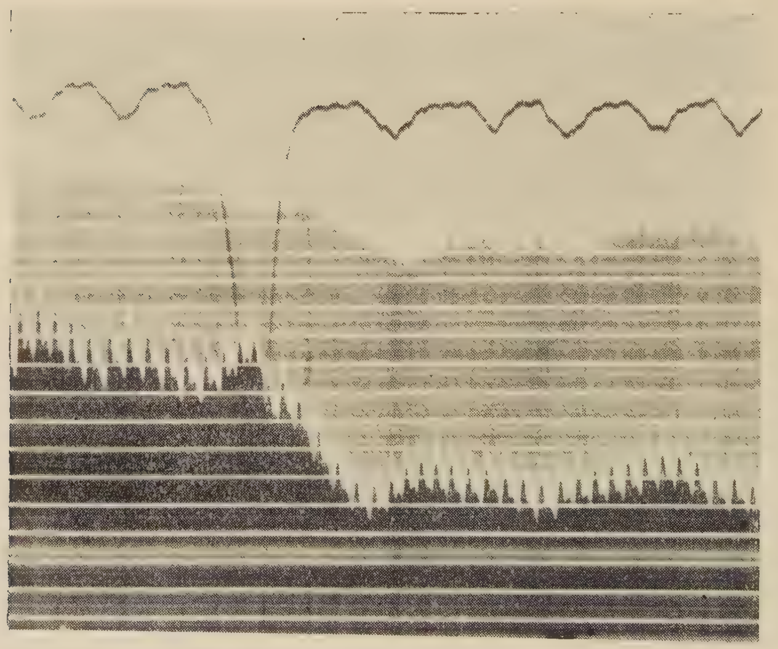
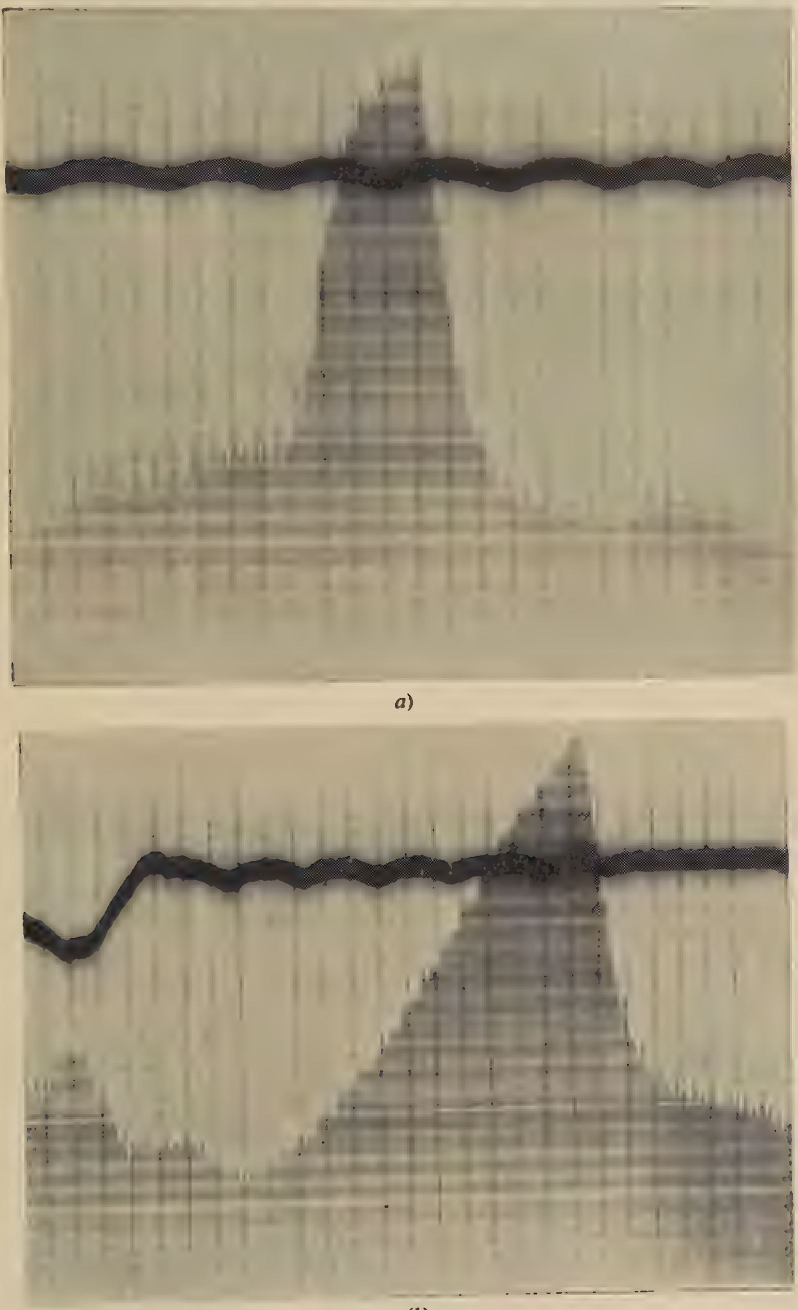


FIG. 8.—Plethysmogram of left index finger (lower tracing) and left big toe (upper tracing). Subject instructed to take one deep breath. Note vasoconstriction in toe as well as finger.

Coinciding with the diminution in pulse volume there is a corresponding reduction in arterial inflow (Fig. 9 (*a*), (*b*) and (*c*)).



*a*)

(*b*)

FIG. 9 (*a*) and (*b*).—Plethysmogram of right index finger during venous congestion tests. Note that in (*a*) the pulse tracing shifts upwards at almost 90 degrees, reflecting a rapid increase in digital volume and consequently a rapid arterial inflow. In (*b*) the tracing moves upwards at an angle of about 45 degrees, showing the slower arterial inflow following the vasoconstriction after one deep breath.

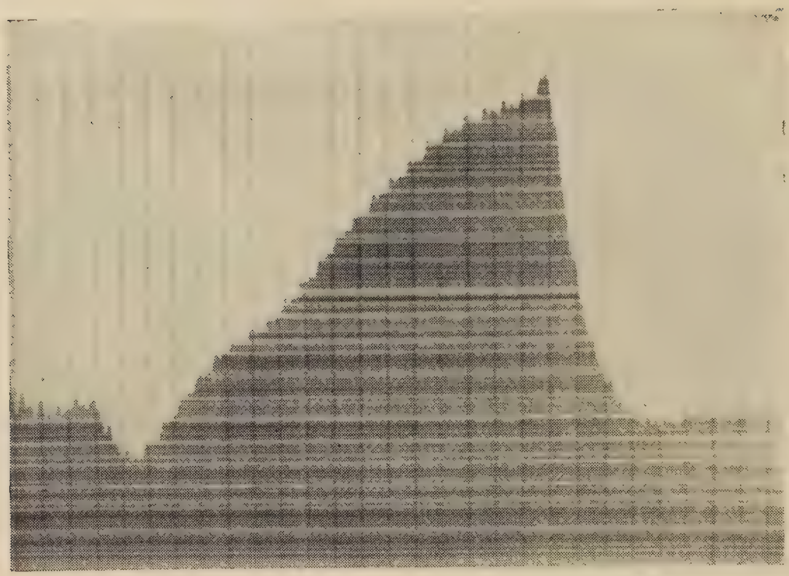


FIG. 9 (*c*).—Plethysmogram of right index finger during venous congestion test after two minutes hyperventilation.

(*b*) This characteristic peripheral vasoconstriction after a deep breath occurred whether air, oxygen or a mixture of air and 4½ per cent. $CO_2$ was breathed (Fig. 10 (*a*), (*b*) and (*c*)).

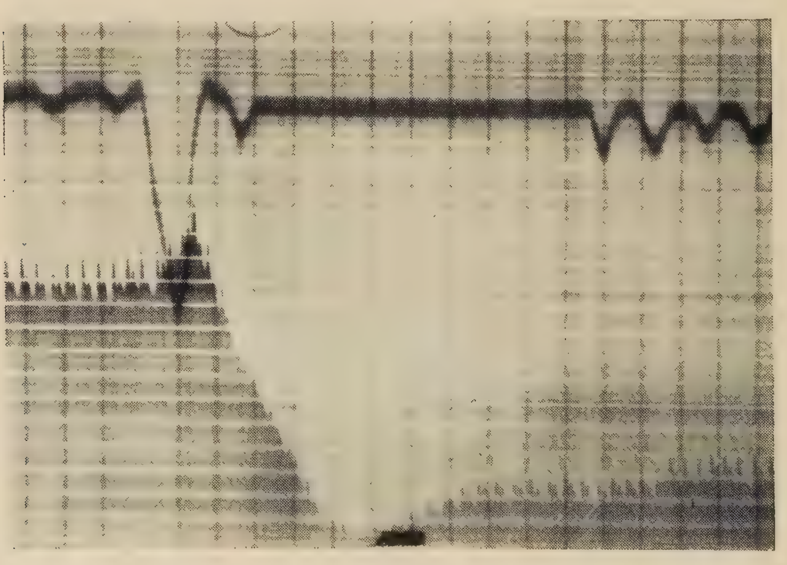


FIG. 10 (*a*).—Plethysmogram of left index finger. Subject breathing air. One deep breath was taken. The apnoea is voluntary. Note vasoconstriction.

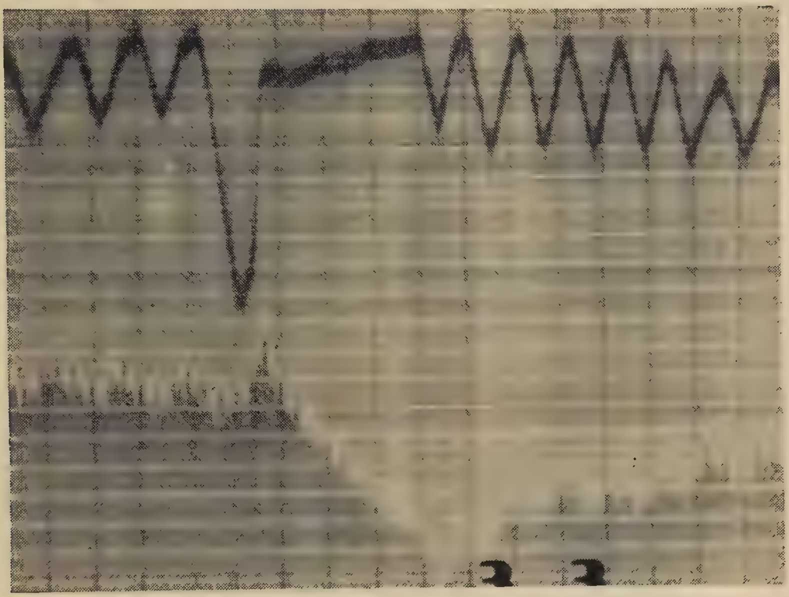


FIG. 10 (*b*).—Plethysmogram of left index finger. Subject breathing a mixture of air and $CO_2$ ($4\frac{1}{2}$ per cent.). One deep breath taken. The apnoea is voluntary. Note vasoconstriction. Also note the appearance of spontaneous fluctuations in digital and pulse volume. The same subject was used for Fig. 10 (*a*) and Fig. 10 (*b*). Both tracings were recorded during the same experiment.

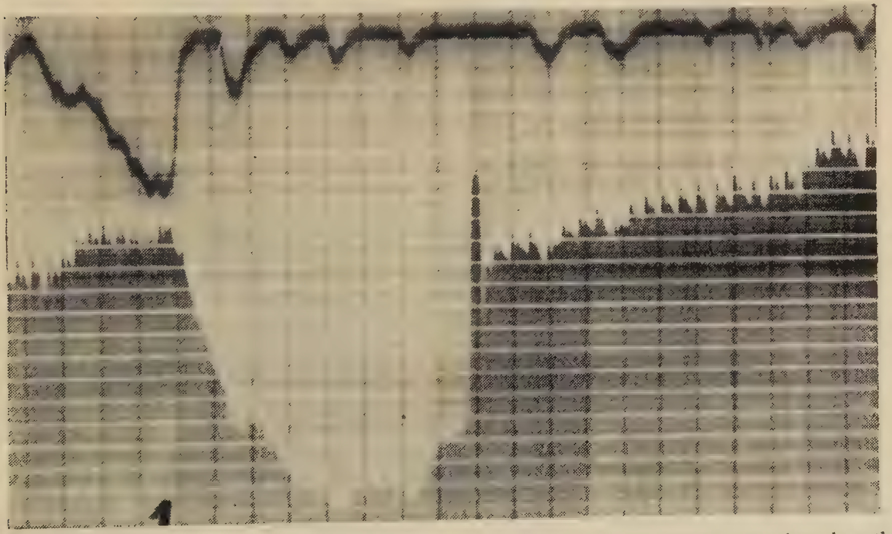


FIG. 10 (*c*).—Plethysmogram of left index finger. Subject breathing oxygen. One deep breath taken. Note vasoconstriction.

It also occurred if the inspired gas was warm and moist or cold and dry. This latter point is of some importance as a cold stimulus to the sensitive nasal mucous membrane sometimes produces a reflex vasoconstriction.

(*c*) The depth of breath is important. Vasoconstriction did not occur with a deeper than normal but still fairly small breath (Fig. 11 (*a*) and (*b*)). It did occur, however, with rapid, shallow breathing (Fig. 12).

(*d*) Vasoconstriction did occur with an attempt to take a deep breath against a closed glottis (Fig. 13).

(*e*) Vasoconstriction did not occur with a purely abdominal breath. This is not surprising because the breath taken in this way was always a small one.

(*f*) Vasoconstriction did not occur in limbs to which the sympathetic supply had been removed. This supports the commonly accepted view that the efferent path for the vasoconstrictor reflex is the sympathetic (Fig. 14 (*a*) and (*b*)).

(*g*) The response to a single deep breath was compared in eight normals and eight hyperventilators. Subjects were matched for age and sex as far as possible (Table I).

TABLE I

*The Changes in Pulse Volume after a Single Deep Breath in Normal Subjects and in Hyperventilators*

| Normal Subjects | Normal Pulse Volume ml. | Pulse Volume after 1 Deep Breath ml. | Duration of Change in Pulse Volume sec. | Normal Respiratory Rate Breath/min. | Normal Pulse Rate Beats/min. |
|---|---|---|---|---|---|
| L. | 0·018 | 0·01 | 25 | 18 | 78 |
| D. | 0·012 | 0·007 | 20 | 24 | 72 |
| M. | 0·021 | 0·011 | 43 | 21 | 78 |
| A. | 0·012 | 0·006 | 25 | 12 | 72 |
| P. | 0·008 | 0·004 | 20 | 18 | 90 |
| S. | 0·025 | 0·012 | 60 | 24 | 72 |
| WC. | 0·013 | 0·005 | 20 | 20 | 72 |
| C. | 0·012 | 0·004 | 30 | 24 | 72 |
| Average | 0·0151 | 0·0073 | 30·3 | 20·1 | 75·7 |
| Hyper-ventilators | | | | | |
| Wi. | 0·006 | 0·003 | 25 | 21 | 78 |
| A. | 0·005 | 0·002 | 20 | 21 | 78 |
| K. | 0·01 | 0·005 | 12 | 18 | 78 |
| B. | 0·01 | 0·005 | 20 | 18 | 90 |
| H. | 0·005 | 0·003 | 20 | 24 | 78 |
| R. | 0·01 | 0·002 | 30 | 24 | 84 |
| M. | 0·011 | 0·005 | 35 | 18 | 66 |
| N. | 0·01 | 0·005 | 30 | 18 | 72 |
| Average | 0·0083 | 0·0037 | 24 | 20·2 | 78 |

A summary of the results shows that, in normals, the average initial pulse volume was 0·0151 ml., a single deep breath reduced this to 0·0073 ml., and this vasoconstriction persisted for an average of 30 seconds. In hyperventilators the average initial pulse volume was 0·0083 ml., a single deep breath reduced it to 0·0037 ml., and this vasoconstriction persisted for an average of 24 seconds.

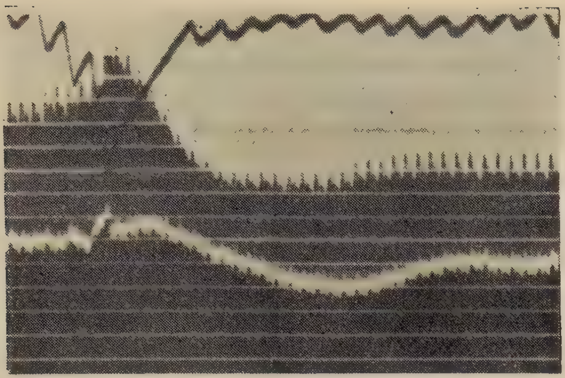


FIG. 11 (*a*).—Plethysmogram of left index finger (upper tracing) and left big toe (lower tracing). One deep breath taken. Note the vasoconstriction.

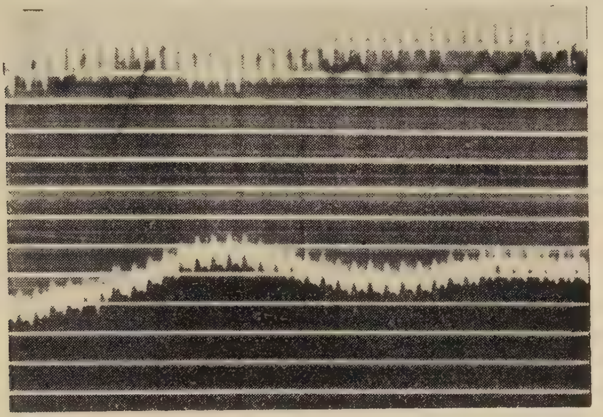


FIG. 11 (*b*).—Plethysmogram of left index finger and left big toe. Subject used was the same as in Fig. 11 (*a*). Both tracings were recorded during one experiment. Subject instructed to take a moderately deep breath. No vasoconstriction occurred.

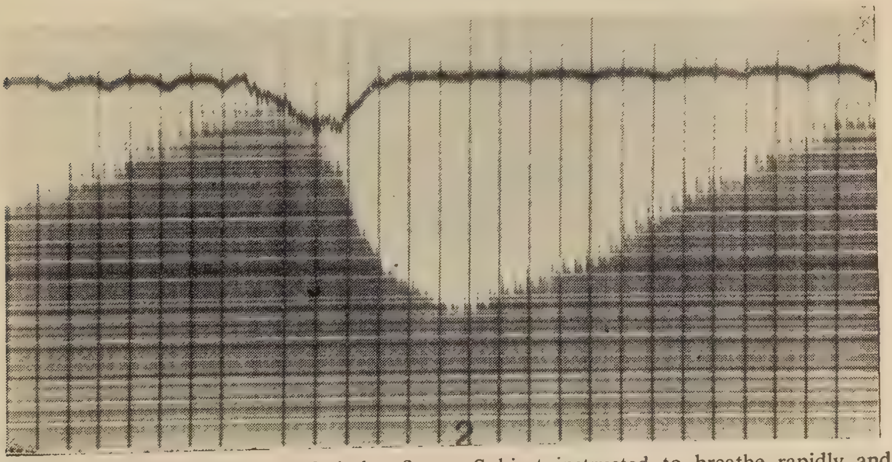


FIG. 12.—Plethysmogram of left index finger. Subject instructed to breathe rapidly and shallowly. Note the vasoconstriction.

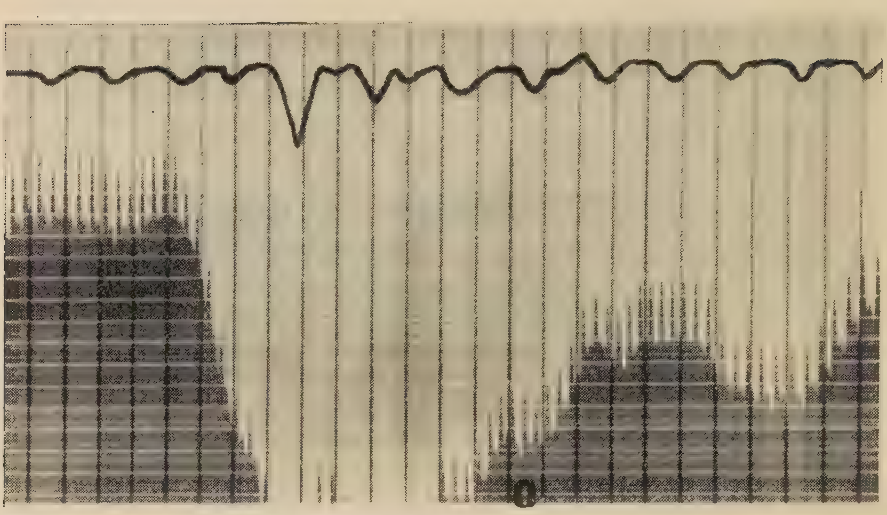


FIG. 13.—Plethysmogram of left big toe. Subject instructed to attempt a deep breath against a closed glottis. Note vasoconstriction and shift in the respiratory tracing indicating the extent of the chest expansion.

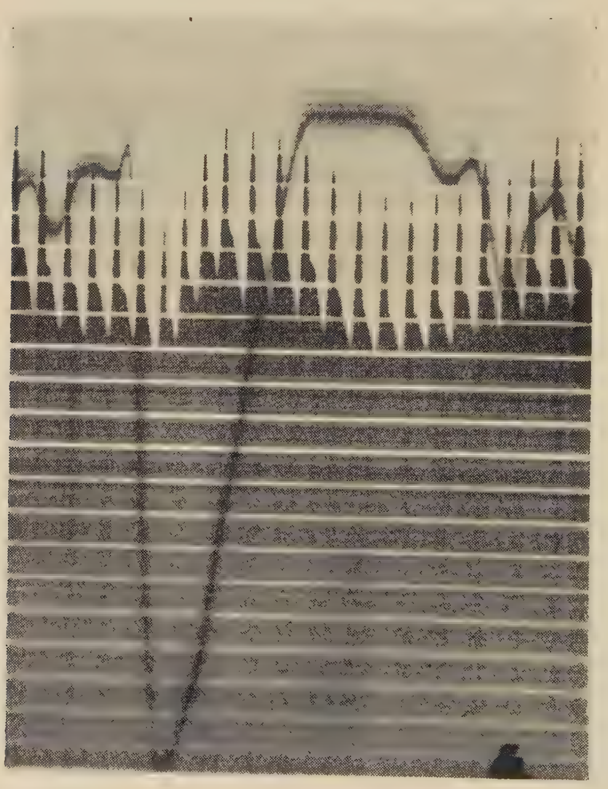


FIG. 14 (*a*).—Plethysmogram of left big toe of a patient who had had a lumbar sympathectomy done a few weeks before the experiment. No vasoconstriction occurred with one deep breath.

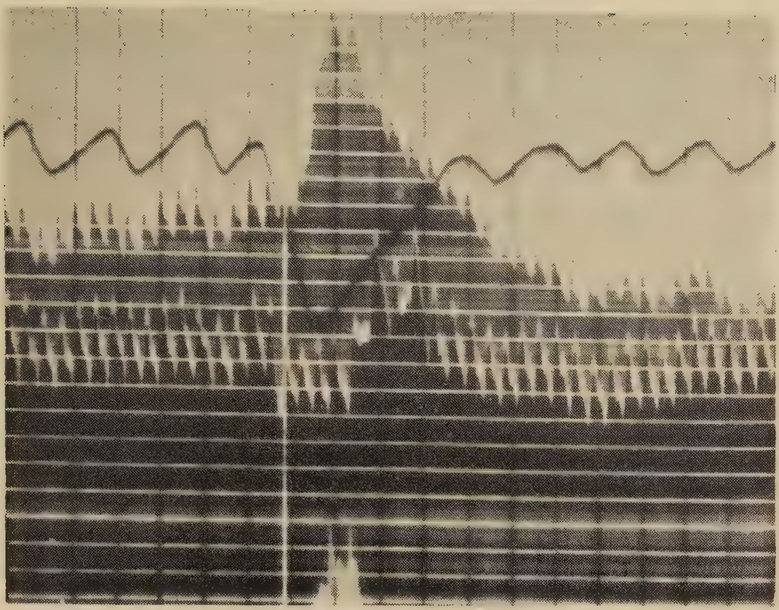


FIG. 14 (*b*).—Plethysmogram of left index finger (upper tracing) and left big toe (lower tracing) of a patient who had had a lumbar sympathectomy several months before the experiment. He had no occlusive vascular disease. Note vasoconstriction occurs in the finger but not in the toe after one deep breath.

*Comment*

A reflex exists whose afferent path is not precisely known. The stimuli that trigger it are: the act of taking a breath of sufficient depth; the act of making an obstructed respiratory effort (where the movement of the chest is nearly as great as that in taking a deep breath); and a series of rapid, shallow breaths. The efferent path is by way of the sympathetic nerve fibres. The response is a vasoconstriction which reduces peripheral pulse volume to less than half of its initial height and reduces the rate of arterial inflow. This peripheral vasoconstriction persists for an average of 30 seconds.

In normals and in hyperventilators the reflex vasoconstriction after a deep breath has the same characteristics. The only striking difference between the two groups is that the average hyperventilator has generally a smaller pulse volume than the normal subject so that any procedure that produces vasoconstriction causes a considerable reduction in peripheral blood flow.

### 2. *The Effect of 2 Minutes of Overbreathing*

The time period of 2 minutes was chosen because previous experience had shown that some of the subjects developed tetanic spasm if they hyperventilated for longer. This broke the seal of the plethysmograph and interrupted the experiment.

Subjects were instructed to breathe deeply at a rate of 30 to 40 breaths per minute. A metronome was tried initially to regulate the rate exactly but was later abandoned because it introduced the factor of mental activity. The depth was not regulated because to achieve this too complicated a procedure is required.

The same subjects were used as those in the first series of experiments.

The Table shows the results obtained and the graph illustrates some of the points (Table II, Fig. 15).

TABLE II

*The Changes in Pulse Volume after 2 Minutes of Overbreathing in Normal Subjects and in Hyperventilators*

| Normal Controls | L. | D. | M. | A. | P. | S. | Wc. | C. | Average |
|---|---|---|---|---|---|---|---|---|---|
| Pulse volume .. | ·005 ml. | ·006 ml. | ·005 ml. | ·004 ml. | ·002 ml. | ·01 ml. | ·005 ml. | ·006 ml. | ·0051 ml. |
| Pulse rate .. | 102 | 90 | 105 | 108 | 105 | 84 | 90 | 78 | 95·2 |
| Respiratory rate and character .. | 21 with *no* apnoeic periods. | 12 with many apnoeic periods. | 18 with apnoeic periods. | 21 with *no* apnoeic periods. | 20 with apnoeic periods. | 18 with numerous periods of apnoea. | 14 with numerous periods of apnoea. | 20 with periods of apnoea. | 18 with 7 out of 8 showing apnoea. |
| Persistence of respiratory abnormality .. | 4 mins. | 2 mins. | 2·5 mins. | 3 mins. | 3 mins. | 2·5 mins. | 2·5 mins. | 3 mins. | 2·8 mins. |
| Persistence of vasoconstriction | 4 mins. | 3 mins. | 4 mins. | 3 mins. | 4 mins. | 1·5 mins. | 3·5 mins. | 3 mins. | 3·2 mins. |
| Hyperventilators | Wi. | A. | K. | BX. | H. | R. | M. | N. | Average |
| Pulse volume .. | ·004 ml. | ·0018 ml. | ·003 ml. | ·004 ml. | ·003 ml. | ·005 ml. | ·005 ml. | ·004 ml. | ·0039 ml. |
| Pulse rate .. | 96 | 120 | 102 | 108 | 96 | 90 | 78 | 90 | 97·5 |
| Respiratory rate and character .. | 15 with apnoeic periods. | 24 with *no* apnoea. | 15 with apnoeic periods. | 17 with *no* apnoea. | 30 with *no* apnoea. | 27 with *no* apnoea, grossly irregular. | 24 with *no* apnoea. | 24 with *no* apnoea. | 23 with 2 out of 8 showing apnoea. |
| Persistence of respiratory abnormality .. | 2·5 mins. | 3·5 mins. | 4 mins. | 3 mins. | 7 mins. | 4 mins. | 3 mins. | 3 mins. | 3·7 mins. |
| Persistence of vasoconstriction | 4 mins. | 5·5 mins. | 8 mins. | 6·5 mins. | 10 mins. | 3 mins. | 6 mins. | 3 mins. | 5·7 mins. |

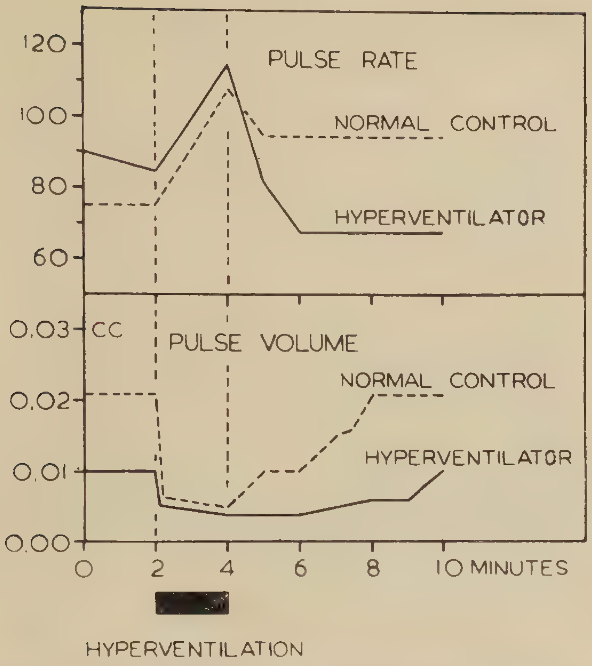


FIG. 15.—This illustrates the change in pulse rate and pulse volume of a normal control and a hyperventilator after 2 minutes of overbreathing. Note the small initial pulse volume and the persistence of vasoconstriction in the hyperventilator.

The normal controls finished their 2 minutes of hyperventilation with:

(*a*) An average pulse volume of 0·0051 ml.
(*b*) A persistence of this vasoconstriction for an average of 3·2 minutes.
(*c*) An average pulse rate of 95 beats per minute.
(*d*) A respiratory tracing that in six of eight cases was notable for periods of apnoea of several seconds duration.
(*e*) A persistence of the abnormal respiratory rhythm for an average of 2·8 minutes.

The hyperventilators finished their 2 minutes of overbreathing with:

(*a*) An average pulse volume of 0·0039 ml.
(*b*) A persistence of this vasoconstriction for an average of 5·7 minutes.
(*c*) An average pulse rate of 97 beats per minute.
(*d*) A respiratory tracing that in only one case showed any evidence of apnoea and in some cases showed an increase in depth compared with the breathing before hyperventilation.
(*e*) A persistence of the respiratory abnormality for an average of 3·7 minutes.

The hyperventilators after 2 minutes of overbreathing have a smaller peripheral blood flow than the normal controls. In addition, this vasoconstriction persists much longer. The interpretation of the pathogenesis of the vasoconstriction after 2 minutes of overbreathing is more complicated than that following a single deep breath.

Two factors complicate the results:

1. A circulatory factor, manifesting itself in a tachycardia. Presumably this results from the physical exertion of overbreathing.

In both the normal controls and the hyperventilators this increase varied between 6 and 30 beats per minute and persisted in both groups for about 1 minute. It cannot therefore be invoked to explain any difference between the two groups as far as degree and persistence of vasoconstriction are concerned.

It is, however, interesting to compare the response of a sympathectomized patient with the effects of the 2 minutes of overbreathing.

In this type of case, the reflex vasoconstriction in response to deep breathing does not occur because its motor path has been removed. A diminution in pulse volume nevertheless does occur, and is correlated with the tachycardia (Figs. 16 and 17).

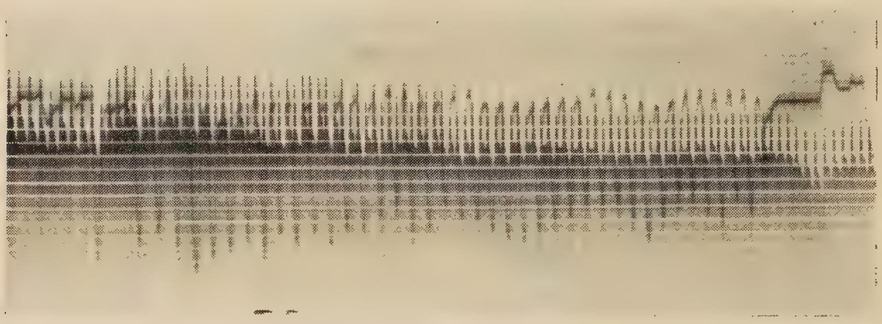


Fig. 16.—Plethysmogram of the left big toe of a patient who had had a lumbar sympathectomy several months before this experiment. One minute of hyperventilation is illustrated. Note that a diminution in pulse volume occurs. This is due to the tachycardia.

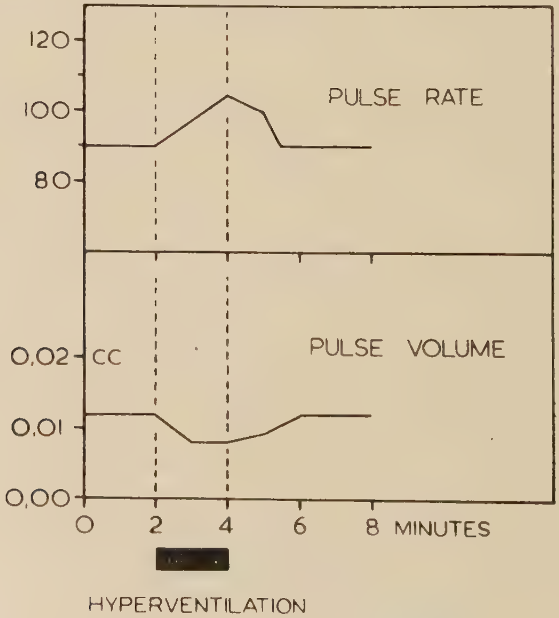
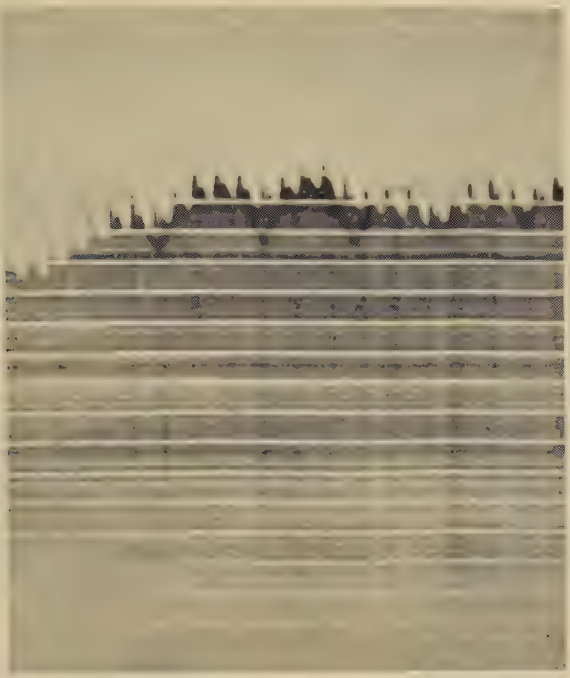
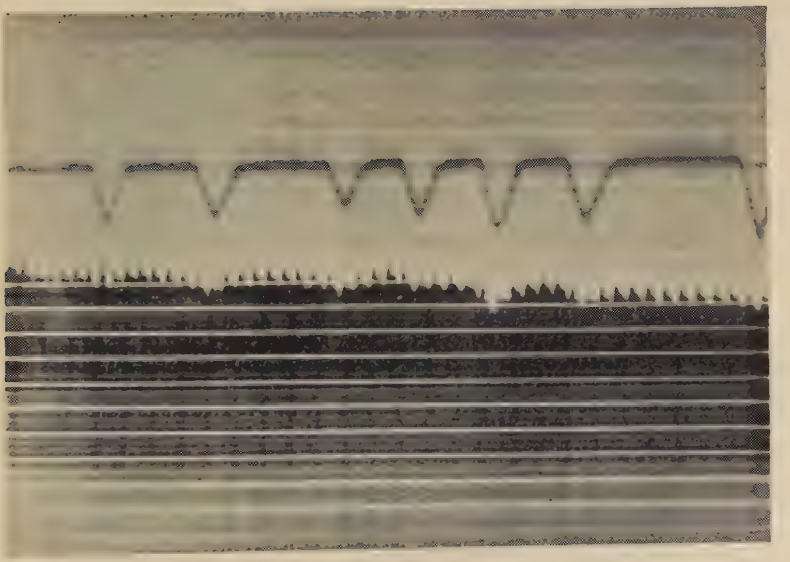


Fig. 17.—This shows the correlation between change in digital pulse volume and change in pulse rate after 2 minutes of overbreathing in a patient in whom the sympathetic chain had been completely removed.

2. The type of respiration after a period of hyperventilation is important. Six of the normal controls showed a slowing of respiration due to many apnoeic pauses (Fig. 18).



(*a*)



(*b*)

FIG. 18 (*a*) and (*b*).—Respiratory tracing of a normal subject: (*a*) before 2 minutes hyperventilation and (*b*) after 2 minutes hyperventilation. Note apnoeic periods in (*b*).

This abnormality persisted for 2 to 3 minutes. The remaining two normal controls immediately resumed normal breathing but at a slightly slower rate.

Four of the hyperventilators continued to breathe much more deeply than before hyperventilation (Fig. 19).

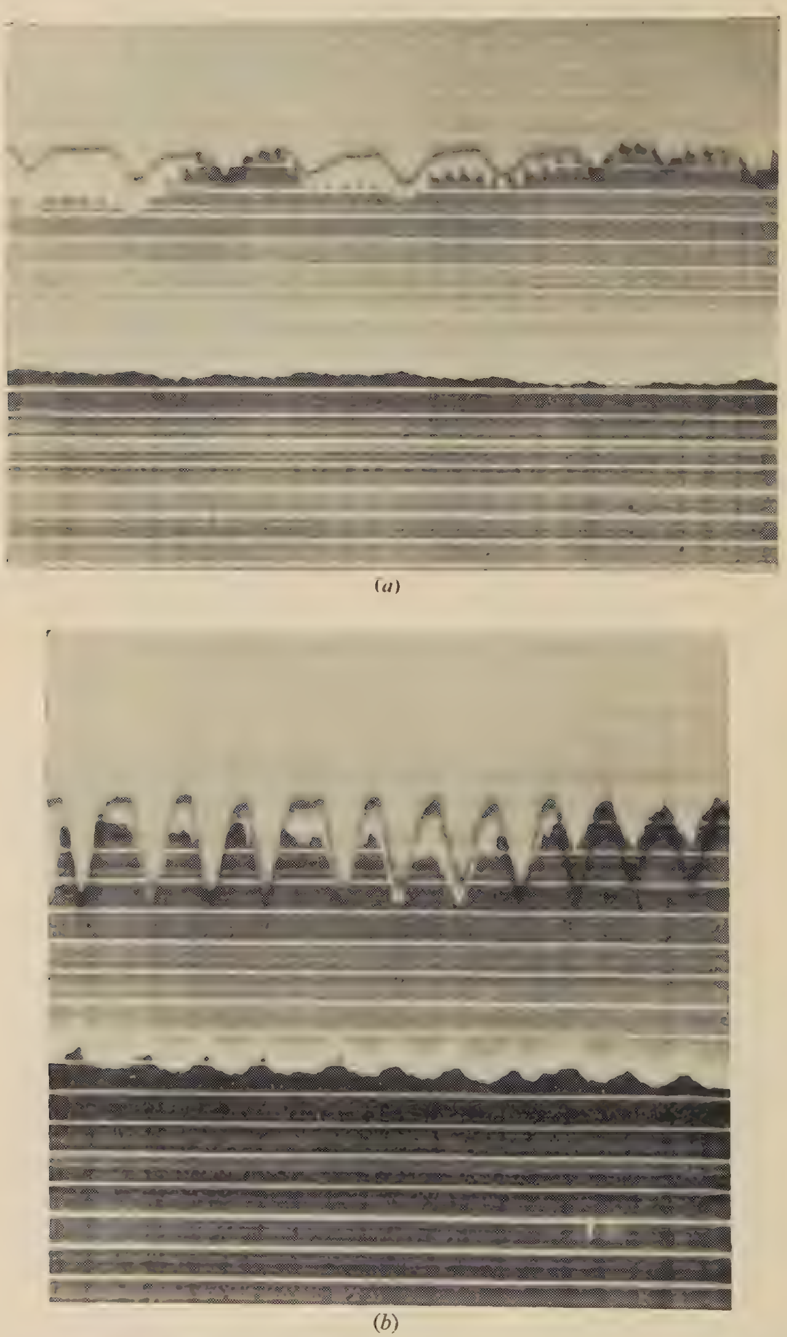


FIG. 19 (*a*) and (*b*).—Respiratory tracing in a hyperventilator: (*a*) before 2 minutes hyperventilation and (*b*) after 2 minutes hyperventilation.

One patient showed a grossly irregular respiration with many periodic deep breaths and spells of rapid, shallow breathing.

Two patients resumed normal breathing but at a slightly slower rate.

Only one patient showed any apnoea and he spontaneously remarked that he had consciously held his breath after the experiment because the whole mechanism of hyperventilation with its consequent physiological changes had been previously explained to him.

The respiratory abnormality in the hyperventilators persisted for 3 to 4 minutes.

It is obvious that the first five hyperventilators would tend to remain in a state of vasoconstriction longer than the normal controls by virtue of the increased depth of their breathing, or periodic deep breaths.

The remaining three patients had, however, no respiratory cause for a lengthy persistence of vasoconstriction after hyperventilation. Two of these cases had a vasoconstriction that lasted 6 and 8 minutes respectively. This may be due to a more rigid vasomotor tone than in normal subjects.

### 3. *The Effect of Hyperventilation*

(*a*) In ten normal controls with one hand warm and the other cool.
(*b*) In ten normal controls with the limbs elevated.
(*c*) In two patients at varying intervals after a two-stage sympathectomy of the upper limbs.

(*a*) Ten normal controls free of any organic vascular disease were used for this experiment.

Both hands were simultaneously immersed in water—one hand at a temperature of 57° F. and the other at a temperature of 110° F. If the water was made too hot or too cold the subjects experienced discomfort in the hands which interfered with their accurate observation of the paraesthesiae resulting from hyperventilation.

The hands were immersed for $1\frac{1}{2}$ minutes. They were then dried by the experimenter. The subject was then seated comfortably with the hands resting lightly on a table. Care was taken to ensure that there was no pressure on peripheral nerves. The subject then began to hyperventilate at a rate of about 35 breaths per minute. The time and place in which paraesthesiae manifested themselves were noted. The experiment was repeated the following day with the hands interchanged (Table III).

It was found that if the experiment was repeated too soon—that is some hours later—the hand in which paraesthesiae had been most intense during the first experiment always tingled first in the second experiment. It appears that the irritability of the peripheral nerve induced by overbreathing may persist for a considerable time—certainly several hours.

From Table III it can be seen that in seven of the ten subjects hyperventilation resulted in paraesthesiae in the cold hand first—whether that hand was the right or the left. In one subject the temperature of the hands did not seem to make any difference as he developed paraesthesiae simultaneously in both the cold and warm hand, after overbreathing for a few minutes. In one subject paraesthesiae always appeared first in the left hand whether it was warm or cool. In one subject paraesthesiae always appeared first in the right hand whether it was warm or cool.

*Comment*. It seems therefore that in most people local cooling of a hand will hasten the appearance in that hand of the paraesthesiae resulting from overbreathing.

### TABLE III

*Times of Onset of Paraesthesiae in Ten Subjects who were Instructed to Hyperventilate with One Hand Cooled and the Other Warmed. The Hand that was Initially Cooled is put First*

| Subject | Cold hand | Results during Hyperventilation |
|---|---|---|
| I. | (i) Left | After 2 minutes left hand began tingling.<br>After 5 minutes no tingling in right hand but cerebral discomfort so marked that the experiment was stopped. |
| | (ii) Right | After 2 minutes right hand began tingling.<br>After 4 minutes no tingling in left hand. |
| V. | (i) Right | After 4 minutes right hand began tingling.<br>After 5 minutes left hand began tingling. |
| | (ii) Left | After 3 minutes left hand began tingling.<br>After 4 minutes right hand began tingling. |
| L. | (i) Right | After 2 minutes right hand began tingling.<br>After 3½ minutes left hand began tingling. |
| | (ii) Left | After 2 minutes left hand began tingling.<br>After 5 minutes no tingling in right hand. |
| S. | (i) Left | After 1 minute left hand began tingling.<br>After 3½ minutes right hand began tingling. |
| | (ii) Right | After 2 minutes right hand began tingling.<br>After 3 minutes left hand began tingling. |
| M. | (i) Right | After 1½ minutes right hand began tingling.<br>After 2½ minutes left hand began tingling. |
| | (ii) Left | After 1½ minutes left hand began tingling.<br>After 2½ minutes right hand began tingling. |
| D. | (i) Left | After 3 minutes left hand began tingling.<br>After 3½ minutes right hand began tingling. |
| | (ii) Right | After 4 minutes right hand began tingling.<br>After 5 minutes left hand began tingling. |
| A. | (i) Right | After 2 minutes right hand began tingling.<br>After 2½ minutes left hand began tingling. |
| | (ii) Left | After 1½ minutes left hand began tingling.<br>After 2 minutes right hand began tingling. |
| M. | (i) Left | Bilateral tingling more intense in left hand. |
| | (ii) Right | Bilateral tingling equally intense in both hands. |
| L. | (i) Left | After 2 minutes left hand began tingling.<br>After 3½ minutes right hand began tingling. |
| | (ii) Right | After 2 minutes left hand began tingling.<br>After 3 minutes right hand began tingling. |
| W. | (i) Left | After 1 minute right hand began tingling.<br>After 2 minutes left hand began tingling. |
| | (ii) Right | After 2 minutes right hand began tingling.<br>After 3 minutes left hand began tingling. |

Two of the subjects were right and left handed dominant as far as the onset of paraesthesiae was concerned. The point has already been mentioned in the clinical section that in some people the site of the initial tingling is always the same. This local susceptibility does not seem to depend on any vascular factor and it is apparently strong enough to overrule any temperature differences.

(*b*) The effect of hyperventilation in elevated limbs.

Ten normal controls free of any organic vascular disease were used for this experiment. The subject lay on the floor with the head on a pillow. One leg was extended and the other elevated at an angle of about 75 degrees. The heel rested against the side of a padded couch. One arm was supported by the observer without compressing any peripheral nerves. The other arm was extended at the side of the subject. This posture was maintained for 2 minutes to accustom the subject to it. The subject then began to overbreathe and reported on the development of paraesthesiae.

From Table IV it can be seen that in eight subjects paraesthesiae first became manifest in the elevated leg; in one subject in both hands; and in one subject in the non-elevated arm. In no subject did the elevated arm tingle first though in three cases it took second place to the elevated leg. Four subjects were unable to complete the experiment despite their recumbent attitude. They found the unnatural position of the limbs too trying when allied with the usual unpleasant symptoms of hyperventilation.

TABLE IV

*Times of Onset of Paraesthesiae in Ten Subjects who were Instructed to Hyperventilate while One Leg and One Arm was kept Elevated*

| Subject | Limb Elevated | Result during Hyperventilation |
|---|---|---|
| L. | Left leg<br>Right arm | After 1 minute tingling began in left leg.<br>Atfer 2 minutes tingling began in right arm.<br>After 4 minutes tingling began in right leg. |
| S. | Left leg<br>Right arm | After 5 minutes tingling began in left leg.<br>After 6 minutes tingling began in right arm. |
| D. | Left leg<br>Right arm | After 1 minute tingling began in left leg.<br>After 3 minutes no tingling anywhere else.<br>Cerebral symptoms so marked that refused to continue overbreathing. |
| W. | Left leg<br>Right arm | After 2 minutes tingling began in left leg.<br>After 4 minutes tingling began in right arm. |
| V. | Right leg<br>Left arm | After 3 minutes tingling began in right leg.<br>After 4 minutes tingling began in left leg. |
| M. | Right leg<br>Left arm | After 2 minutes tingling began in right leg.<br>After 3 minutes tingling began in left leg.<br>After 3½ minutes tingling began in left arm.<br>After 5 minutes tingling began in right arm. |
| LO. | Right leg<br>Left arm | After 3 minutes tingling both hands.<br>After 5 minutes too uncomfortable to continue. No paraesthesiae in feet. |
| A. | Left leg<br>Right arm | After 3 minutes tingling began in left leg.<br>Subject too uncomfortable to continue overbreathing. |
| T. | Right leg<br>Left arm | After 2 minutes tingling began in right arm.<br>After 3 minutes tingling began in right leg. Subject too uncomfortable to continue overbreathing. |
| M. | Right leg<br>Left arm | After 2 minutes tingling began in right leg.<br>After 3 minutes tingling began in both hands.<br>After 4 minutes tingling began in left leg. |

*Comment.* Elevation of the leg hastens the onset of the paraesthesiae resulting from hyperventilation. This is remarkable because normally with the subject recumbent the legs are often late in manifesting paraesthesiae.

(*c*) The effect of hyperventilation in two patients at varying intervals after a two-stage sympathectomy of the upper limbs.

1. This patient was a European female of 20 years who suffered from acrocyanosis. She was an excellent witness. The experiment was performed 5, 7, 13 and 24 days after the right arm had been adequately sympathectomized.

(*i*) After 5 days:

The right arm was warm and dry, the left cold and blue.

The patient lay recumbent and began to overbreathe at about 35 breaths per minute. She was told to report any unusual sensations immediately. She reported as follows:

After 2 minutes: tingling in right hand;
3 minutes: coldness in left hand;
4 minutes: the whole right arm tingling markedly;
5 minutes: jaw tingling;
10 minutes: tingling started in left hand;
15 minutes: right arm felt numb and "dead";
25 minutes: subjective stiffness of the right hand and adduction of the thumb—commencing tetanic spasm. At this time there was only slight tingling in the left hand.

Throughout the experiment the right hand remained warm and dry while the left hand became progressively colder and sweated profusely.

(*ii*) After 7 days:

The experiment was repeated. The patient reported:

After 2 minutes: dizziness;
3 minutes: tingling in right hand;
4 minutes: tingling in legs;
6 minutes: slight tingling in left hand. (At this stage the patient began to yawn uncontrollably and continued to do so till the end of the experiment);
9 minutes: a lame, tingling feeling in the whole of right arm and still slight tingling in the left hand;
15 minutes: tingling increased in left hand;
17 minutes: tetanic spasm commenced in right hand.

(Throughout the experiment the right hand remained warm and dry while the left hand became progressively colder and sweated profusely.)

(*iii*) After 13 days (and 6 days after the left arm had been sympathectomized): at this time both hands were warm and dry. The patient had some slight tingling in the left ulnar distribution, probably the result of traction on the brachial plexus during the second operation.

She reported:

After 1 minute: dizziness;
3 minutes: both hands tingling;
5 minutes: both legs tingling;
6 minutes: uncontrollable yawning;
7 minutes: her whole body twitching;
12 minutes: continued to yawn and felt sleepy;
13 minutes: whole of left arm tingling much more markedly than the right side;
16 minutes: left arm felt "very funny—sort of lame and tingly".
20 minutes: left arm still tingled markedly, a little tingling of right hand.

(*iv*) After 24 days (and 17 days after the left arm had been sympathectomized): at this time both hands were warm and dry and the slight tingling in the ulnar distribution had diminished. The patient breathed at 40 breaths per minute—reasonably deeply.

She reported:

After 3 minutes: dizziness;
4 minutes: pain in chest;
5 minutes: slight tingling in both hands—more intense in left ulnar nerve distribution;
10 minutes: generalized shivering and feet felt very cold;
11 minutes: slight tingling in both forearms;
16 minutes: both legs tingling;
18 minutes: both arms felt "dead";
26 minutes: both arms tingling and legs felt "dead";
28 minutes: hands and feet tingling markedly and fingers "stiff";
44 minutes: tingling sensation wore off in hands, except in the left ulnar nerve area, legs still tingling slightly and feet cold and sweating, face and ears tingling markedly. She remarked that the tingling was much less than on previous occasions. There was no motor spasm throughout the experiment.

*Comment*. The first two tests were carried out 5 days and 7 days after the right arm had been sympathectomized. Twenty minutes of overbreathing resulted in the appearance of tetanic spasm in the right hand with moderate paraesthesiae in the left hand.

The third test was carried out 13 days after the right and 6 days after the left arm had been sympathectomized. On this occasion the left hand developed marked paraesthesiae with minimal tingling in the right hand.

The fourth test was carried out 24 days after the right and 17 days after the left arm had been sympathectomized. On this occasion paraesthesiae of moderate intensity developed in both hands. This wore off later despite continued hyperventilation and never progressed to tetanic spasm.

In other words the subject with an established sympathectomy was much less susceptible to the manifestations of peripheral nerve irritability resulting from hyperventilation than is a normal subject. Forty-four minutes of reasonably vigorous hyperventilation in a normal subject will almost certainly produce well-marked tetanic spasm in the arms.

The transient increase in susceptibility of the sympathectomized limbs a few days after the operation could be explained by postulating a temporary irritability of the peripheral nerves as a result of traction on the brachial plexus at operation. This does occur and did so in this case because the patient had symptoms of left ulnar nerve irritation.

2. This was a European female of 28 years who was suffering from acrocyanosis.

(*i*) The first experiment was done pre-operatively. The patient was very apprehensive. She reported as follows:

After 1 minute of overbreathing: markedly dizzy;
3 minutes: felt cold (her whole body began to shiver);
7 minutes: tingling in both hands—much more intense on left side.

She refused to continue hyperventilation.

Her hands at the onset of the experiment had been blue and cold and became progressively colder and sweated profusely.

(*ii*) Experiment was repeated 11 days after the left arm had been sympathectomized. She did not have a Horner's syndrome. The left hand was warm and dry and the right cold and blue.

She began to hyperventilate at 36 breaths per minute and flexed her legs because she could "breathe better".

After 2 minutes: giddiness;
5 minutes: tingling began in right hand;
6 minutes: her teeth began chattering but she said she was not very cold;
11 minutes: "lameness" in left hand—but no tingling;
14 minutes: right hand tingling markedly;
16 minutes: feet began to tingle;
21 minutes: right arm and both feet tingling markedly;
24 minutes: right hand stiff and felt "terrible";
26 minutes: tetanic spasm right hand. At this time the left hand felt normal apart from slight "lameness".

Twenty days after the left arm had been sympathectomized and 6 days after the right arm had been sympathectomized:

After 3 minutes: dizziness;
6 minutes: both feet tingling markedly;
7 minutes: generalized shivering;
9 minutes: slight laryngeal stridor;
11 minutes: marked stridor—became extremely anxious and semi-conscious with thrashing around of her limbs. The experiment was stopped.

*Comment*. This woman differed from the previous patient in that the sympathectomy was not so extensive—she did not develop a Horner's syndrome as the stellate was not completely removed.

Before her operation hyperventilation resulted in paraesthesiae in both hands—more marked on the left side. Eleven days after the left arm had been sympathectomized 26 minutes of hyperventilation resulted in tetanic spasm of the right hand and paraesthesiae in the legs. In the left hand there was only slight "lameness".

Twenty days after the left arm had been sympathectomized and 6 days after the right arm had been sympathectomized 11 minutes of overbreathing resulted in paraesthesiae in both feet but no change in the hands. Laryngeal stridor terminated the experiment.

A comparison of her reactions before and after sympathectomy shows that the operation made her upper limbs less vulnerable to the peripheral nerve signs resulting from hyperventilation. She did not show the transient increase in susceptibility that the first case showed. This can be attributed to the fact that the operation, being less extensive, did not interfere with the brachial plexus.

## Discussion

It has become evident that a great deal of illness is of emotional origin and that all illness has its emotional component.

The hyperventilation syndrome is one of the ways in which emotional stress becomes manifest. An attempt has been made to study, not only the clinical manifestations, but also some of the physiological mechanisms invoked by overbreathing. It is felt that an understanding of the physiological background of an emotionally engendered illness will lead to a much clearer conception of the, at present, vaguely understood entity of "psychosomatic medicine".

Hyperventilation results from a stimulus to the respiratory centre. The manner in which this stimulation is brought about is not precisely known but it is in some way connected with stress.

The purpose of the hyperventilation is a preparation for motor activity. Symptoms result when this motor activity is restrained by the inbuilt social and cultural inhibitions of the individual. The remarks of Russell (1952) on experimental neuroses are pertinent here. He says: "The precipitating factor is conflict, but another essential factor present in all the successful experimental techniques, is restraint of voluntary movements, either by a harness, or by the subject's own learned patterns of movement."

It is interesting that most patients in this series found that they were unable to keep still during hyperventilation and that even purposeless movements relieved their symptoms to some extent. But, in the absence of co-ordinated motor activity, the main effect of the overbreathing was turned back on the body, causing physical disturbance. This physical dysfunction was manifested in all systems of the body, but neurogenic dysfunction gives the hyperventilation syndrome its specific stamp.

Most of the patients were aware of respiratory dysfunction, but not that they were hyperventilating. The commonest complaint was that of not being able to get a satisfactory breath and this referred particularly to the depth of the breath. This respiratory difficulty is characteristically unrelated to exertion.

Once hyperventilation was established, the commonest group of symptoms were those of central nervous system disturbance. These comprised cerebral disturbances which, though rarely gross enough to result in loss of consciousness, were nevertheless distressing to the patient. They comprised dizziness, visual disturbance, feelings of unreality, etc. They may be associated with electro-encephalographic changes. There is a reduction in cerebral blood flow of about 30 per cent.

Peripheral nerve involvement was manifested by paraesthesiae, starting in hands and feet and later becoming generalized. A few cases progressed to tetanic spasm.

The commonest gastro-intestinal disturbance was distension of the stomach which resulted from air-swallowing during overbreathing.

Circulatory disturbances comprised praecordial pain, palpitations and coldness of the extremities. Two patients complained of a diuresis. Fatigue was a common symptom.

The signs and symptoms were enhanced if the patient was emotionally disturbed, in fact if stress was present.

At least three separate physiological mechanisms are invoked as a direct result of overbreathing.

These are:

1. An increased alkalinity of the blood.
2. A reflex peripheral vasoconstriction.
3. Circulatory effects resulting from the muscular exercise of overbreathing.

1. The increased alkalinity of the blood which results from loss of $CO_2$ during hyperventilation is of primary importance. Patients who overbreathe a $CO_2$ rich mixture do not develop the characteristic symptoms of neurogenic dysfunction. Conversely many of the symptoms of this syndrome are rapidly relieved by re-breathing $CO_2$. It is the alkalosis that:

(*a*) Increases neuromuscular irritability to the point where tetany may develop.

(*b*) Causes cerebral blood vessels to constrict. This conserves their low $CO_2$ content.

(*c*) Renders haemoglobin reluctant to part with its oxygen thereby interfering further with the nutrition of the tissues and especially of nerve tissue.

2. Reflex peripheral vasoconstriction is an integral part of the hyperventilation syndrome. It accounts for the cold extremities, the sweating and the pallor. To Henderson (1909) these features were so striking that he described at length the "shock-like" state seen after prolonged overbreathing.

It has been shown that the motor route for this reflex is along the sympathetic nerve fibres. The afferent path is not precisely known but seems to be connected in some way with expansion of the chest or lungs. The vasoconstriction after several minutes of overbreathing persists for many minutes and tends to persist longer in hyperventilators. This can be only partially explained by the type of respiration after hyperventilation in these subjects, and an additional factor, which is a less easy adaptability of their vasomotor tone, has been suggested.

If hyperventilation is assumed to be part of the physiological preparation for flight or attack, what is the significance of the reflex peripheral vasoconstriction? It seems reasonable to assume that, like the effect of adrenaline, it is part of a general vascular shift to supply the skeletal muscles with additional blood. Limb plethysmography is notoriously difficult to interpret, as so many tissues are included in the plethysmograph that it becomes difficult to assign to any one tissue any specific change in blood supply. With the digital plethysmograph one is, for all practical purposes, dealing only with skin. Eichna and Wilkins (1941) studied the changes in the volume of the forearm and calf after various stimuli which are known to produce skin vasoconstriction, e.g. deep breath, noise, mental activity, etc. By far the commonest response was a moderate decrease in limb volume. Occasionally the limb increased in volume, either moderately or markedly.

We know that with one deep breath a marked skin vasoconstriction is produced. If the limb as a whole usually shows only a moderate decrease in volume and occasionally even an increase in volume, it seems reasonable to assume that the relatively large quantity of blood being diverted from the skin is being accommodated elsewhere in the limb and that it is probably muscle tissue which is receiving the extra blood.

Clarke (1952) claimed that during moderate over-ventilation (20 per minute for 3 minutes at maximum depth) there is a two-fold increase in blood flow to the forearm. He attributed this to vasodilatation in the muscles and thought that it resulted from the hypocapnia.

The next question that arises is whether this assumed redistribution of blood in the limbs during overbreathing plays any part in the genesis of the peripheral neurological symptoms and signs of the hyperventilation syndrome? Evidence that it plays some part is the fact that procedures designed to interfere with the normal reflex distribution of blood with overbreathing can alter the speed of development and the intensity of the manifestations of peripheral nerve irritability.

Cooling a hand or elevating a limb, especially the leg, usually accelerates the onset of paraesthesiae, whereas sympathectomizing a limb has the opposite effect.

Cooling a hand presumably increased the intensity of the reflex peripheral vasoconstriction. The effect of elevating a limb is more complicated as shown by Goetz in 1950. He demonstrated striking alterations in the vascular supply to a limb during elevation.

These are:

(1) An increase in the systolic elevation and a decrease in the dicrotic wave of the pulse.

(2) An accentuation of the changes in digital volume resulting from extrinsic stimuli, e.g. noise, deep breath, etc.
(3) A delayed response to reflex body heating.
(4) A drop in skin temperature.

These changes were attributed to an acceleration of the venous return from the limb. They are more marked in the legs because the venous return from the legs is considerable.

The acceleration of the onset of paraesthesiae with elevation is probably due to the fact that all the tissues in the limb have a less effective blood supply during elevation because of the rapidity of the venous return.

Removal of the sympathetic supply to a limb abolishes the reflex peripheral vasoconstriction of deep breathing. In two cases of upper limb sympathectomy the paraesthesiae of hyperventilation were tardy in appearing and much less intense once the sympathectomy had become established. This effect was strikingly illustrated in one case where the opportunity arose of recording the patients' response to overbreathing pre-operatively.

The next question, and this can only be dealt with very speculatively, is how precisely this vascular factor works.

We know that a reflex peripheral vasoconstriction of the skin occurs. This will interfere with the vascular supply of the nerve terminals. But the crucial question appears to be whether there is a change in vascular supply to the peripheral nerve itself. This is not known at present, but if the general vascular shift in the limb is to supply the skeletal muscles, then the peripheral nerve may suffer with the skin in depletion of its blood supply.

Ischaemia itself is a potent agent in increasing the irritability of peripheral nerves. Lewis, Pickering and Rothschild (1933) demonstrated this, and the generally accepted explanation of the Trousseau phenomenon is that it activates the nerve through ischaemia (Lewis, 1942). Neuromuscular tissue functions less well when cold, e.g. myotonic spasm is often precipitated by cold.

It is the alkalosis which is of primary importance in the pathogenesis of the peripheral nerve irritability. This is emphasized by the fact that after 2 minutes of overbreathing, although the vasoconstriction persists for about 3 minutes, the paraesthesiae disappear in about 1 minute. Nevertheless, these investigations indicate that the peripheral vasoconstriction does in some way lower the threshold of nerve irritability, and so contributes to the manifestations of the hyperventilation syndrome. The factor of ischaemia may also be of importance in the genesis of the tetany of hypocalcaemic patients. One case of this (resulting from steatorrhoea) was seen and she spontaneously remarked that cold precipitated many of her attacks and she could often avert an impending attack by warming her limbs.

3. The effect of overbreathing purely as a form of muscular exercise is another factor of importance. This has only been touched on. All patients who overbreathed for 2 minutes developed an increase of heart rate ranging from 6 to 30 beats per minute. This lasted for about 1 minute after the cessation of overbreathing. One patient in the series, who presented with "palpitations" as her major complaint, regularly produced a pulse rate of 120 beats per minute after a few minutes of overbreathing. This tachycardia also occurs in sympathectomized patients after hyperventilation and explains the diminution in pulse volume which develops despite the absence of reflex peripheral vasoconstriction.

A fourth factor which must receive mention because of the role of stress in the hyperventilation syndrome is the factor of adrenaline release. Although its direct study is outside the scope of this thesis it must be considered as a possible background factor because of its action as a respiratory stimulant; its effect in causing skin vasoconstriction and muscle vasodilatation and its influence in upsetting ionic equilibrium. Although adrenaline release does not appear to alter the symptoms and signs of the hyperventilation syndrome in a qualitative sense, it probably plays a part in enhancing or maintaining the physiological effects of the other 3 factors.

Although the factors of alkalosis, reflex peripheral vasoconstriction and circulatory effects from muscular effort and adrenaline release are separate and distinct they are intricately interwoven to produce a highly specific clinical picture which we recognize as the hyperventilation syndrome.

## Summary and Conclusions

1. A study has been made of the hyperventilation syndrome, the name given to a group of symptoms and signs which result from overbreathing.

In this thesis the view has been taken that the hyperventilation is a physiological preparation for fight or flight. Certainly emotional stress is responsible for most cases of the syndrome. Physical dysfunction arises because the patient, though physiologically prepared for some form of motor activity, is inhibited by social or cultural traditions from carrying his emotional response over into a motor response.

2. The literature on the effects of overbreathing in man has been reviewed.

3. The clinical symptomatology of forty patients with this syndrome has been analysed. Neurogenic dysfunction, both central and peripheral, gives the syndrome its distinctive character but involvement of other systems, especially the circulatory one, is often prominent.

4. The criteria for diagnosis, the value of a hyperventilation test and differential diagnosis have been discussed.

5. Treatment consists of explaining the mechanism of hyperventilation to the patient, demonstrating the reproduction of symptoms by overbreathing and the relief of symptoms by re-breathing a carbon dioxide rich atmosphere or by breathholding. The idea is to break at one point the physiological chain of reactions of the emotional response.

Long-term treatment is aimed at relieving emotional stress by discussions with the patient and by teaching him the technique of progressive relaxation.

6. The experimental section enquires into the peripheral vasoconstrictor effect of overbreathing. This is an integral part of the syndrome.

The peripheral vasoconstriction is reflex and mediated through the sympathetic pathway. The afferent path is not precisely known but it is evoked by the act of taking a deep breath, making an obstructed respiratory effort, or by rapid, shallow breathing. It occurs with a carbon dioxide rich mixture as well as with air or other gases. The reduction in pulse volume is considerable. Digital volume and arterial inflow are also reduced.

7. Plethysmographic studies of eight normal controls and eight members of the series of cases described, show that this reflex peripheral vasoconstriction has the same characters in both groups.

The only difference between them is that the hyperventilators tend, clinically and plethysmographically, to be cold-handed, so that any vasoconstrictor stimulus will reduce their peripheral blood flow to a lower level than that of a normal subject responding to the same stimulus.

8. The following changes produced by 2 minutes of overbreathing have been investigated in eight normals and eight hyperventilators.

(a) *Reflex peripheral vasoconstriction.* In normal subjects this vasoconstriction persisted for about 3 minutes after termination of 2 minutes of overbreathing. In the hyperventilators the vasoconstriction persisted for about 5 minutes. The high vasomotor tone of the hyperventilators might be partly responsible for the longer duration of the vasoconstriction.

(b) *An increase in pulse rate.* This varied markedly in both normal subjects and hyperventilators. The range of increase was from 6 to 30 beats per minute. This increase in pulse rate also occurred in sympathectomized patients. It caused a diminution in their pulse volume after 2 or more minutes of overbreathing.

(c) *Abnormal respiration.* In six of the eight normal subjects the respiration after 2 minutes of hyperventilation was characterized by periods of apnoea. In the hyperventilators apnoea occurred in only one case; in four cases the respiration actually increased in depth compared with that before hyperventilation; in one case it was grossly irregular.

9. Investigations were undertaken to see whether the time of onset and intensity of the symptoms of peripheral nerve irritation were influenced by changes in the vascular supply to the limbs. The manœuvres carried out for this purpose were:

(a) *Cooling one hand and warming the other.* In seven of ten cases local cooling accelerated the onset of the paraesthesiae.

(b) *Elevating a limb.* This accelerated the onset of paraesthesiae in the leg in eight of ten cases.

(c) *Sympathectomized upper limbs.* Sympathectomy delayed the onset and diminished the intensity of paraesthesiae in both the cases investigated.

10. The syndrome is discussed with particular reference to the mechanisms brought into operation by overbreathing.

These are:

(*a*) An alkalaemia produced by the blowing off of $CO_2$. This produces a cerebral vasoconstriction, reducing blood flow in the brain by as much as 30 per cent. It causes peripheral nerve irritability which manifests itself as tetany. It also interferes with tissue oxidation.

(*b*) A reflex peripheral vasoconstriction which is responsible for the cold hands, sweating, etc. It is considered as part of a general vascular shift to supply the skeletal muscles with more blood. It is assumed that the peripheral nerve, as well as the skin, has its blood supply curtailed.

Consequently the peripheral nerve is not only subjected to the exciting influence of the alkalosis, but this excitation is enhanced by the ischaemia resulting from the reflex peripheral vasoconstriction.

Manœuvres that accentuate this ischaemia, such as local cooling or elevation of a limb, accelerate the onset of symptoms of peripheral nerve irritation. Conversely, sympathectomy, which abolishes the reflex peripheral vasoconstriction, delays the onset of these symptoms. It is pointed out that after several minutes of hyperventilation the peripheral pulse volume in sympathectomized limbs is also ultimately reduced. This diminution in pulse volume is closely correlated with the tachycardia that occurs after overbreathing.

(*c*) Circulatory effects produced by the muscular exercise of overbreathing.

Most patients get an increase in heart rate after several minutes of overbreathing. This varies widely between 6 and 30 beats per minute. In some patients who get a considerable increase in heart rate "palpitations" is a major complaint.

Fatigue, which is a very common complaint, is probably partly caused by the muscular work of overbreathing.

(*d*) There may be a background factor of emotional stress which, when present, enhances the symptoms and signs.

## Appendix of Case Histories

This appendix summarizes forty cases individually. In all of them, except Case 20, the symptoms and signs were reproduced by hyperventilation. Case 20 was too apprehensive to risk precipitating laryngeal stridor by overbreathing.

Case 18 is given in more detail than the others, not only because it is so representative of the syndrome but because the patient was an extremely reliable and intelligent observer.

E.M. stands for European male.
E.F. stands for European female.
C.M. stands for Coloured male.
C.F. stands for Coloured female.

### 1. *J.N.—36 years (E.M.)*

This patient was an epileptic. He said that for about 2 years he had been rather worried because of his epileptic attacks and because of domestic tension. During this period he often got a feeling "as though his chest had closed in" and he felt compelled to rush out of the house to get fresh air. These attacks lasted about 10 minutes.

One week before coming to hospital he got this feeling of not getting enough air. It was so acute that he actually tore his collar open "to let in the air". He then became very dizzy and staggered "like a drunk man" clutching a fence to keep on his feet. He was not conscious of any paraesthesiae. This attack lasted about 45 minutes.

Three weeks later he reported back to out-patients to say that he had started to get an attack like his previous one but had immediately breathed into his hat and within a few minutes all his symptoms had disappeared.

### 2. *S.B.—42 years (E.F.)*

The patient stated that she was perfectly well until 6 months before our interview. One night, while preparing for bed, she developed a "funny feeling over my heart as though something had stopped there". When she got into bed a few minutes later she got a "dead feeling" in all the fingers of her left hand and a cold feeling in the left ear and over part of the left side of her face. Her head felt "drunk". She thought she was having a "heart attack" and got very frightened. She woke her husband, who gave her some brandy and the attack passed off. She said the whole thing lasted about 10 minutes and that when she got the cold feeling in the left ear she tested her hearing with a clock and found it defective on the left side. She was not conscious of any respiratory abnormality and her husband did not remark on any "but then he is so nervous that he would be too upset to notice anything clearly". Since that time she had had one or two attacks per month—always when she had just gone to bed and if she had had a worrying day. She had to sit up in bed when she got the attacks. Fatigue also precipitated attacks.

The only abnormality discovered on examination was mild diabetes. A hyperventilation test carried on for 8 minutes reproduced all the symptoms including objective diminution of hearing on the affected side. Pulse rate increased from 90 to 120. She said that her heart always beat fast with the attacks.

3. *Mrs. W.—22 years* (*E.F.*)

This woman complained that for about 3 months she had been getting a "tight feeling in her chest" and she felt she had to get outside to get fresh air. Associated with this she would get a stabbing feeling in the left praecordium and her heart would beat very fast. On one occasion she developed "pins and needles" in her fingers and her hands got stiff. She thought she always breathed fast on these occasions "but the doctor told me that was just imagination". Her hands had been clammy for some time. During the last 2 years she had lost about 20 lb. in weight but said it was due to her poor appetite. She preferred cold weather but did not find hot weather intolerable. She was admitted to hospital as a case of thyrotoxicosis and her B.M.R. was found to be raised.

She had been married for 4 years and had three children. "If I had not been pregnant I would never have married my husband." The marriage was very unsatisfactory. He lived apart in a hotel except at weekends and was unfaithful to her.

4. *Mrs. W.—29 years* (*E.F.*)

Her trouble had lasted 5 years. She had noticed that if she became upset her breathing would become quick and shallow. She would become giddy and would feel a numbness creeping up her arms and round her mouth. The attacks lasted a few minutes.

When she became pregnant two years later the attacks recurred. They never wakened her from sleep but often occurred before she fell asleep. She was particularly prone to get attacks if she was very tired or worried about anything.

She had a lot of financial and domestic trouble and was terrified of having more children.

5. *G.S.—37 years* (*E.F.*)

This patient complained that for the previous 3 weeks she had experienced periodic attacks of giddiness associated with a "pins and needles" sensation in the right hand. She was not conscious of any respiratory difficulty at these times but had always been a prodigious sigher. In addition, she felt tired all the time. She was afraid to climb stairs in case she got a giddy turn and fell.

She was a widow with three children and had always lived with her mother until a few months before. She felt lonely without her mother and was obviously very dependent. She mentioned spontaneously that it was her mother's absence which was making her ill.

6. *W.C.—24 years* (*E.M.*)

This patient had had a mastoidectomy and then became worried that his other ear was also affected. He haunted E.N.T. surgeons and was constantly and very transiently reassured. At that time he began to get attacks when in bed about 11 p.m. The first attack consisted of giddiness and a tingling sensation in the left ulnar distribution. He would then get a fishy-taste in his mouth and a sharp pain under the sternum which shot up to his shoulder and round his neck. He also got a sharp pain in his left hypochondrium and if he palpated his abdomen would hear a "lot of gurgling". The attacks lasted 10 to 15 minutes and then he would be unable to sleep without a sedative.

7. *B.C.—54 years* (*E.M.*)

This man was a constant visitor to Neurology O.P.D. because of tinnitus in both ears. He had no sign of organic disease apart from arteriosclerosis and as he was worried about being unemployed a job was found for him. However, he reported back the following week to say he could not go to work "because whenever I have to cross the road I get so dizzy that I fear I will fall and I get pins and needles in my fingers and toes".

8. *E.D.—48 years* (*E.F.*)

This woman had been extensively investigated for palpitations. Her story was that suddenly her heart would "race furiously", she would feel slightly nauseated and breathless and her left hand would start tingling. She had been put to bed for months at a time and had had numerous cardiovascular investigations. She was convinced that she had "a bad heart". All investigations were negative and one day during a ward round attention was directed to her because of loud breathing. On examination her pulse rate was 134/minute and she gasped "this is one of my attacks". She was quite unaware of the fact that she was overbreathing.

9. *M.B.—29 years* (*C.F.*)

Her story was that a year before seeking medical advice her daughter had died suddenly in the night "from a tuberculous gland bursting in her throat". For 8 months the patient, who was herself under observation at the T.B. Clinic because of a past pleural effusion, had been getting nocturnal attacks during which she suddenly became very apprehensive, felt "a tight feeling in the throat", so that she could not breathe properly, but gasped for breath. Associated with this she felt strange and unreal and was so terrified and restless that she would run out into the lonely street at 3 a.m. with her heart racing. The attacks lasted about 30 minutes and afterwards she had a feeling of extreme fatigue.

10. *Mrs. B.—45 years (E.F.)*

This patient had had several attacks when bad news had been brought to her. One day while sitting in a bus she felt very short of breath and could not think straight. After a few minutes she had marked tingling in her extremities and felt very dizzy. She felt she must get out of the bus and asked the conductor to let her off. She spoke thickly because her mouth felt stiff and she was markedly ataxic. He thought she was drunk and refused to stop the bus. In desperation she jumped off and he threatened to charge her.

She also tended to get attacks when she got very hot, e.g. when cooking over a hot stove. She had several burn marks on her arms from occasions when, in a confused state from hyperventilation she had swayed against the hot plates.

To complicate matters she had a congenital heart lesion and was convinced that these attacks were a result of her cardiac lesion especially as she had been made respiration conscious by medical interrogation.

11. *Mrs. R.—38 years (E.F.)*

This woman complained of constant headaches which were considered to be psychogenic. In addition, she was irritable and sensitive to sound. Sometimes when she had a bad headache she got a feeling as though she was suffocating. Then the fingers of her left hand would begin to tingle. She also said her left arm got "lame". She was greatly relieved when this feeling was reproduced in the left arm by hyperventilation because she was sure it had meant that she was going to get a "stroke".

12. *M.S.—20 years (E.F.)*

This woman had suffered from dysmenorrhoea for several years and from a spastic colon for several months. She said that during the few months before our interview she would get a feeling as though she could not get enough air into her chest. This happened most frequently on retiring for the night. Then she would get a tingling feeling in both hands, especially the left, her legs would feel lame and her mouth so "thick" that she could not speak properly. Attacks lasted about 15 minutes. They also occurred during the day when she got nervous and excited and she occasionally "fainted" with them.

She had a bad work record—due she said to sickness—and her home atmosphere was not good. She was very resentful about her mother's preference for her young sister.

She was sure she had a bad heart because during the attacks her heart beat so fast and "several doctors have told me these attacks are due to a weak heart".

13. *T.W.—17 years (E.F.)*

This girl complained that for two years she had been short of breath on exertion and thought there was something the matter with her chest. Four days before she came to hospital she had to run for her train. On getting into the train she was short of breath. Alarm about her chest resulted in persistent overbreathing for the next 20 minutes while she sat in the train. As the train drew into the station she felt light-headed and was so peculiar "that hardly knowing what I was doing I pulled open the door and fell from the moving train". When she arrived at work she was so shaky and tearful that she was sent home. Two minutes of hyperventilation reproduced the same light-headedness and desire for flight.

14. *W.K.—17 years (E.M.)*

This boy said he had been perfectly well until 2 months before our interview. One Saturday night he was sitting on the stoep with a crowd of young people when he suddenly felt dizzy, then became confused and when he came to a few minutes later found his friends holding him down. Six weeks later on a Sunday night under the same circumstances "I suddenly felt that I must get more fresh air. My right arm began to tingle and as I got up to walk out I collapsed. I could hear everything that went on around me but could not speak or move. They carried me home and I had three more attacks that night. People always knew when I was going to get an attack because my breathing got so deep."

He had been converted to the Salvation Army at the age of ten and had played in their band on Wednesday and Sunday nights regularly for 6 years. Just before his attacks began he had decided that he must have more "fun" and had given up his band playing. However, he felt very guilty about it and both attacks had occurred after taking out a girl.

15. *G.H.—28 years (E.F.)*

This woman was interesting in that the pattern of her symptoms varied so much. At one time she would feel that she had to sigh a lot and things went black in front of her eyes, or she would feel that something was pressing on her chest, and her throat would close in spasm. At other times attacks would start with a "pins and needles" sensation in her hands and later her legs felt stiff and her hands would go into spasm. The left hand was always more affected than the right and her left shoulder would also draw up. She felt that her stomach was drawn up into a knot and she would get distended with air and belch a lot. Her hands became cold and were wet with sweat.

She had had a bad time with an unfaithful first husband and imagined that her second husband was too interested in a previous girl friend. Incidentally she had spent about £200 on her illness and at one time had been thought to be suffering from Jacksonian epilepsy because of the drawing up of the left shoulder.

However, all her symptoms, including the shoulder movement, were reproduced by overbreathing.

16. *W.W.—45 years (E.F.)*

The patient was quite well until two nights before admission to hospital. She was sitting reading a book when she suddenly felt faint and began to sweat. She then became unconscious within a few minutes of the onset of her symptoms. She thinks she was completely unconscious for a few minutes. When she came round she noticed that her thumbs were turned into her palms and this happened in spite of herself. Her fingers were blue and she had a sensation of "pins and needles" up both arms. She rubbed her hands together to overcome the abnormal position of her thumbs and remembers that her hands were not weak. She was sweating profusely, her feet were cold and she was breathing rapidly. She could see quite clearly, but had no nausea and no palpitations. A friend was present during the attack and told her that her face was blue and her pulse impalpable.

On direct questioning she remembers that after her evening meal she had a sensation of a lump behind the sternum—like a dull ache which went through to the back and was relieved slightly by breaking wind. Her mother had died of heart trouble a few weeks before this attack. She had had this substernal discomfort on two previous occasions but never so severely.

17. *J.K.—30 years (Malay woman)*

She complained through an interpreter of attacks for one year. They occurred every 5 or 6 days. An attack usually began about 20 minutes after a meal. It would start with a burning feeling under the sternum. She would begin to breathe heavily and would complain of a pricking feeling in the fingers and a stiffness of the legs. After about 20 minutes she would lie down, turn blue, and become unconscious. Simultaneously her abdomen would become enormously distended.

A hyperventilation test carried out for 30 minutes reproduced the picture exactly. The distension of the abdomen was dramatic and she broke a lot of wind at this time. A striking thing was that she yawned uncontrollably during the experiment which she apparently also did spontaneously. While semi-comatose with a distended belly she began a curious grunting noise with an action strongly reminiscent of bearing down in labour. She developed a gross lumbar lordosis during the attack.

Apparently she had one daughter of 12 years and was desperately anxious to have other children.

18. *M.W.—32 years (E.M.)*

This man stated that 5 weeks before our interview he was driving in Johannesburg at 4.45 a.m. He was on his way to pick up a friend with whom he planned to leave on holiday at 5 a.m. He was worried about being on time, and when a robot flashed against him he became agitated. He felt giddy and everything seemed out of perspective. He began to sweat and his heart was beating like a sledge-hammer. He had a feeling of submersion "as though someone was holding my head under water". Although he could get air into his chest "it was an unsatisfactory breath" and he felt he would die for lack of air. He had a sharp pain over the left breast and a feeling of tension in the muscles of the left forearm.

He immediately thought he had a coronary thrombosis (he had been present at the death of a friend from a coronary thrombosis a few months before) and stopped the car. After a few minutes he drove on to a telephone booth, to which he staggered, but had no change so had to return to the car. He then drove to his friend's flat, holding the door of the car open "so that he could get enough air". He drove through several stop-streets and as he parked at the door of his friend's flat a police car stopped behind him and he was accused of being drunk. He excused himself on the grounds of illness and entered the flat.

His friend was horrified by his pallor, so phoned for a doctor. The doctor reassured him and arranged for him to have an electrocardiogram done immediately. It was normal. His blood pressure was normal and pulse rate 100 beats per minute. He was breathing deeply.

He was told that it was an "anxiety attack" and was advised to go on holiday. The whole attack lasted about half-an-hour.

He left on holiday the following morning and was away for a month. During this period he had attacks very similar to the first only slightly less severe. Attacks occurred at intervals of 2 or 3 days.

All in all he had a miserable holiday and was still extremely apprehensive about himself when he returned to Johannesburg. He consulted a doctor who told him he was suffering from the "hyperventilation syndrome", explained the mechanism and told him to hold his breath if he got symptoms. He was enormously relieved at the logical explanation of his symptoms and felt a lot better. That night he woke up at about 1 a.m. with one of his attacks, and on holding his breath the whole thing passed off and he fell asleep much reassured. Three days later he had a mild attack which was immediately relieved by breath-holding.

The night before our interview he was preparing for bed when he became violently giddy and felt he was going mad. He wondered if he were mad to react to stress by overbreathing. He wanted to scream and took a sedative and after about an hour the attack passed off and he fell asleep. He was not conscious of the old suffocating feeling this time and did not think that breath-holding helped very much.

At the age of 17 he was told when he wanted to take out an insurance policy, that he had nephritis. He was put to bed for a year. Later he was periodically told that he had a high blood pressure and an albuminuria and got the impression that his days were numbered. He was accepted into the Air Force, however, and served as a pilot throughout the war. He never had any symptoms while flying.

About 11 months ago he began to wake up in the middle of the night with "pins and needles" in the left hand and often had nightmares.

He has had a lot of worry about a brother for the last 11 months. He is unmarried. He says he is "obsessional"—e.g. smokes only 8 cigarettes a day and then always at the same time; is very punctilious about keeping appointments; does the same set of exercises every day and must eat at regular times. He has a number of medical friends, some of whom are psychiatrists and has a strong belief in the power of reason and logic.

After three deep breaths he was violently giddy and afraid to continue. In less than a minute he had "pins and needles" in the left hand and a feeling of tension in the muscles of the left forearm. He then got a sharp praecordial pain, a tight feeling round the head and felt very cold and apprehensive. He said that it was an exact reproduction of his attacks.

At his second interview he demonstrated how practically all day he sucked at his pipe for a few minutes, then took a deep breath as he removed it.

19. *G.L.—52 years* (*C.F.*)

This woman complained that for 2 years she had noticed that after even very slight exertion she became short of breath, and experienced a tightness of the chest, sweated profusely and had tingling in her toes and fingers and round her mouth. For 3 months she had been wakened at night by a feeling of discomfort in the epigastrium, associated with profuse sweating and "pins and needles" in the extremities. Her abdomen became distended and subsided after about 10 minutes when she had broken a lot of wind. The whole attack lasted about 30 minutes and occurred about twice a week.

Hyperventilation reproduced all her symptoms, including the epigastric sensation, which seemed to be due to spasm of the abdominal muscles. She had no evidence of organic disease. Her husband had left her 2 years previously and she was having a struggle supporting her children.

20. *E.M.—52 years* (*E.F.*)

This woman had a thyroidectomy 4 years previously. One month after the operation she was recognized as being myxoedematous. During the operation her recurrent laryngeal nerve had been cut. Eight months after operation she had her first attack of laryngeal spasm. This was thought to be due to parathyroid removal at the time of the thyroidectomy. The long time interval between the operation and the attack makes this diagnosis improbable. In any case her serum calcium was normal. She continued to get attacks for years—another unusual feature for the parathyroid type. Her attacks usually occurred at night but occasionally during the day she felt as though she could not get a deep enough breath and her left hand tingled.

Unfortunately she was too afraid of the stridor to risk precipitating an attack by overbreathing, but she was undoubtedly a case of hyperventilation.

21. *P.L.—19 years* (*E.M.*)

This was a second year medical student who complained of a subjective and objective coldness of the extremities coming on during lectures about 4 times a week and lasting several hours. He had had this symptom for a year and on questioning said that for the same period he had had a feeling of not being able to take a deep enough breath, so that he had to breathe through his mouth. During these attacks he sweated excessively and said he got the sensation "as if someone was putting dry ice on his toes and fingers". He thought he had some peripheral vascular disease. He was going through an unsettling time because he had had a strict religious upbringing and was bewildered by his zoological studies, as they seemed to fit the theory of evolution which his parents said was arrant nonsense. His mother had recently developed peripheral vascular trouble. After the mechanism of his attacks had been explained and demonstrated to him by a hyperventilation test he made an immediate recovery.

22. *P.L.—19 years* (*E.F.*)

Her story extended over 3 months. Her first attack occurred just after her pet dog had been killed. It started with a peculiar feeling in the epigastrium "as though her stomach had turned to jelly". She felt she could not get a deep enough breath, felt giddy and her fingers and toes began to tingle. She sweated profusely. The attack lasted 5 to 10 minutes. Two months later when working under stress she had a series of similar attacks. She always had attacks when she was lying on her bed alone thinking about something miserable. She was a conscientious girl and could not cope with work in an understaffed office.

She was referred as a case of hypoglycaemia.

23. *Mrs. R.J.—49 years* (*E.F.*)

This woman complained that for about two years she had suffered from a tight feeling across the upper sternum associated with a tingling feeling in the left hand and a feeling as though she could not get a deep enough breath. The attacks lasted for about 20 minutes and were not necessarily associated with exertion, emotional stress being often the precipitating factor. On several occasions she had felt faint. She was not hypertensive or diabetic and hyperventilation reproduced all the symptoms, including the substernal discomfort.

24. *R.K.—18 years* (*E.F.*)

This girl was referred to Neurology outpatients department as an epileptic. Her story was that 5 days previously she had just returned from church and saw her mother scolding her sister-in-law for some minor misdemeanour when she "suddenly dropped to the ground". Although unable to speak she could hear everything. Since that time she had had several attacks every day—sometimes a bitter taste in her mouth preceded an attack. She had never bitten her tongue or wet herself during an attack. On one occasion she had had some tingling in her hands on "coming to".

She was told to overbreathe, which she did recumbent for 4 minutes without developing any striking symptoms. She was then told to sit up and immediately there was a marked increase in rate and depth of breathing and she fell back semi-conscious with her hands in the tetanic posture. Her mother, watching this, said, "But this is exactly what happens when she gets a fit; she always breathes like that but we did not think it important."

The girl had been converted to some religious group and spent all her spare time doing religious work. Her boy friend, who had been converted with her, had recently deserted both the religious movement and the patient.

25. *B.B.—45 years* (*E.M.*)

For about a year he had had repeated episodes of inability to get "a proper breath". He would writhe and struggle at these times, breathing fast and irregularly. About 3 or 4 times a week he would be awakened at night and forced to jump out of bed and contort his body to get some respiratory satisfaction. Sweat poured off him and his abdomen became distended. He felt light-headed.

When his attacks started he had just remarried a woman he had previously divorced. She was extravagant and was making the lives of his children a misery by her scolding and irritability.

26. *Mrs. S.T.—40 years* (*E.F.*)

This woman was admitted with a sciatic syndrome. She had no other complaints except that on direct questioning she admitted that periodically in the last 3 years she had had a feeling as though she could not get a deep enough breath. This usually occurred when she was upset about her domestic troubles.

On the third day of admission she was lying in bed when she suddenly developed this respiratory difficulty. A few minutes later she felt cold and hot by turn and simultaneously a tingling sensation crept up her legs and arms until her face and trunk were involved. Then her hands went into tetanic spasm.

The nursing staff were alarmed and called the houseman. When he arrived she was overbreathing vigorously, had a positive Chvostek and Trousseau sign, and her neck was stiff. He thought it might be a result of the lumbar puncture which he had done that morning but with reassurance all the patient's symptoms disappeared in about 20 minutes.

The picture was reproduced the following day by overbreathing for 6 minutes.

On enquiry it was found that her husband was unreliable and unfaithful and she was worried about the care of her children because she had not been visited at all since admission.

27. *O.W.—30 years* (*E.F.*)

This woman had had a splenectomy 10 days before she began overbreathing. Her story was that after the operation she felt fine for 5 days. Then she developed watery diarrhoea about 3 or 4 times daily. One night she developed a severe paroxysmal cramp-like pain across the epigastrium. The pain waxed and waned but was present throughout the night. She also vomited repeatedly during the night. The following morning during a bout of pain she became very alarmed about herself and noticed that her hands and face were tingling.

A little later the houseman put on a tourniquet to take blood and missed the vein several times. She again began tingling and the obstructed hand went into typical tetanic spasm. At this time although she herself was unaware of it, it was observed that she was overbreathing. In this case the patient was peculiarly susceptible to the effects of overbreathing because she was already alkalotic from the vomiting.

28. *W.T.—19 years* (*E.M.*)

This patient developed severe abdominal pain and vomiting which subsequently was found to be due to acute appendicitis. Two days after the onset of the pain he suddenly got "a peculiar attack", which consisted of tingling of his face with a "stiff" feeling round his mouth; a few minutes later his body became stiff and his hands assumed the tetanic posture. He said the spasm was acutely painful. A doctor was hastily called and relieved the condition by an injection of calcium gluconate.

For the next 2 days he was free of attacks but still had abdominal pain. On the third day he was sent to hospital for an operation. On the day of admission he had a similar attack although this time his face was spared. He was not aware of any respiratory abnormality though the attack in hospital was ushered in by obvious overbreathing. Alkalosis due to vomiting made him vulnerable in the first attack and emotional stress due to an impending operation was the factor precipitating the second attack when he was not alkalotic.

29. *G.M.—17 years* (*E.F.*)

This nurse said that for about a year she had tended to laugh and cry very easily. Four months before seeking medical advice she had an attack with the following symptoms: she was laughing a lot then suddenly began to cry. She felt she could not get a deep enough breath and began to pant. After a few minutes her hands and feet became numb and "dead" up to the middle of the forearms. The attack lasted for 30 minutes, and was terminated by a doctor giving her a sedative. Three and a half months later she had a similar attack.

On questioning she admitted that she hated nursing but felt that her parents would be angry if she proposed a change of occupation.

30. *E.P.—38 years* (*E.F.*)

This woman was referred from a country town with a diagnosis of thyrotoxicosis. She said that she periodically got attacks when she had difficulty in breathing, developed "pins and needles" in the finger tips, sweated profusely and got palpitations.

She was going through a period of domestic tension.

31. *F.J.—39 years* (*E.M.*)

For 6 months before admission the patient had experienced attacks of coldness, pallor and sweating of the hands. Sometimes the hands felt "dead" and he had a tingling feeling in his face. Associated with this he often experienced a feeling of discomfort in the left hypochondrium which extended up to his chest "as though something was pressing on his heart". Attacks lasted 10 to 30 minutes and he felt blown up and broke a lot of wind, which relieved the discomfort in the left side. He felt a bit short of breath with the attacks. Attacks usually occurred about midnight waking him from sleep. He had been told that his heart was diseased and had been put to bed for 5 weeks.

One month before his symptoms began his sister-in-law, who was asthmatic, died. Throughout her distressing and dyspnoeic final agonies the patient was present and says it made a deep impression on him.

32. *C.K.—26 years* (*E.F.*)

This woman had been getting attacks for about 2 months before she came to hospital.

She said: "When I get the attacks they start with a feeling as though my nose is blocked, so I breathe through my mouth. I feel smothered and I can't get enough air. I feel as though I am going to faint, so go and lie down. All the blood seems to leave my hands. The saliva dries up in my mouth. I get a 'pins and needles' feeling in my arms as far as the elbows and in both feet. I get a stabbing pain over my heart and break a lot of wind. I pass water a lot during the attack and my water is very pale. An attack lasts about 20 to 30 minutes."

She had married her husband when their child was about 2 years old and had been treated unkindly by his family, who did not think she was good enough for him and were constantly interfering in their marriage.

33. *E.M.—19 years* (*C.F.*)

This girl said that she had been well until 10 days before she came to hospital. Then one night as she lay in bed reading she felt she could not get a deep enough breath. She felt giddy and had "pins and needles" in her hands and feet. She had cold shivers and trembled violently. She walked up and down for about 2 hours before the attack finally wore off. Seven days later she had a similar attack at about midnight and was awakened every 1 or 2 hours throughout the night by a recurrence of the symptoms.

She denied all worries but said, weeping, that a favourite aunt of hers had died 3 weeks before.

During 2 minutes of hyperventilation she got exactly the same symptoms and wept profusely.

34. *H.A.—44 years* (*E.M.*)

This man stated that for 3 months before coming to hospital he had been getting attacks when he felt anxious. His breathing became stertorous. He felt a "pins and needles" sensation in his hands and then his hands "drew up" so that he was unable to use them. At the same time he felt faint and unreal "as though mesmerized" and on one occasion actually fell over because of the faintness. Speech became thick and he could not articulate properly. Attacks lasted about an hour and were relieved by neat brandy.

He had always sighed a lot and for several years had been unable to write while observed because of a violent tremor of the hands and a feeling as though he was suffocating; if he was asked to sign a hotel register he felt incapable of doing so and made some excuse about putting the car away so that his wife could do the signing.

A hyperventilation test resulted in marked giddiness and paraesthesiae in both hands with marked tremor of the hands. He refused to continue beyond 2 minutes as he felt so ill.

35. *C.B.—33 years* (*E.M.*)

This man was an immigrant who was "having a hard and bitter fight" to make a living in this country. In addition, his wife had severe asthma; "hearing her struggle for breath at night makes me breathe faster". He sometimes had dizzy spells which were so disturbing when driving that he had to park his car and wait until the attack had passed. His main complaint, however, was of a tight feeling across the upper abdomen, "gripping like a vice", which made him feel that he could not breathe properly. When he had this feeling he was extremely restless and if an attack occurred near a meal time he was forced to eat standing up.

Experimental hyperventilation reproduced the vice-like feeling "exactly".

36. *P.C.—36 years* (*E.F.*)

This woman was very much pre-occupied with a pain in her back which had been extensively investigated on many occasions in hospital. She had had a Halsted operation some years before for a suspected mammary carcinoma, and was convinced that the pain was due to a secondary deposit. She eventually became a chronic hospital inmate and if discharged would hyperventilate herself into a state of semi-coma and have herself re-admitted as a "coma of unknown origin".

37. *M.B.—18 years* (*E.F.*)

This girl was a nurse who was sitting talking to her friends round the fire one evening when she became aware of a feeling of numbness in her hands and feet. She got up to leave the room and while walking across the room got "lame" in her legs and collapsed. She was carried to bed and after a few minutes her hands and feet assumed the tetanic posture. She was not conscious of overbreathing but said a friend of hers was alarmed when they were sitting in front of the fire "because her breathing was so deep". She continued to have tetanic spasm throughout the night. The next morning she had marked muscle tenderness and a "feeling of lameness in her legs".

She was admitted to the City Hospital as suspected poliomyelitis.

She denied any worries, but the fact that she was due to go home on leave the next day was thought to be of some significance.

38. *A.M.—38 years* (*E.M.*)

This patient developed a left-sided hemiplegia—due to a vascular accident. One month after this he experienced an attack which he described thus: "I woke up one morning and found my left hand in spasm. I had a tingling feeling on the left side of my mouth. Then my left leg got stiff. My wife had to massage me for about 15 minutes before the spasm passed off. I don't think I was breathing fast, but my wife says I always breathe too deep."

He hyperventilated experimentally for about 30 minutes and then developed well-marked tetany in the left hand which was present for a good 20 minutes before there was any sign of tetany on the other side. Incidentally apart from slight weakness on the left side and a positive finger flexion and Hoffman he had very little evidence of a hemiplegia. Hyperventilation did not bring out any additional pyramidal signs.

39. *J.D.—34 years* (*E.M.*)

This man was in hospital with a proven duodenal ulcer. One morning he developed a sharp pain "like a knife" in the left praecordium. He asked for the houseman who was busy and was fairly casual about the pain. About 30 minutes later the patient developed tingling in the left ulnar distribution and "broke out in a cold sweat". His feet and hands then became "dead" and he could not move his limbs or open his eyes. He could hear the medical staff talking round his bed but could not speak. Witnesses say he was breathing heavily at the time though he was quite unaware of this.

40. *E.F.—18 years* (*C.F.*)

This girl came to hospital complaining of "blackouts" which occurred about 3 times a week, especially when she was in crowds. She never became unconscious but during the attack she had difficulty in seeing properly and sounds seemed far away. In addition she breathed fast and her hands were wet with sweat.

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# OLOLIUQUI: THE ANCIENT AZTEC NARCOTIC

## REMARKS ON THE EFFECTS OF *RIVEA CORYMBOSA* (OLOLIUQUI)*†

By

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### INTRODUCTION

THIS is an account of a model psychosis (6) produced by eating the seed of a tropical American plant which is known in Mexico as ololiuqui. It is only quite recently that Schultes (16) has made order from chaos in the matter of the identity of a climbing vine called *Rivea corymbosa.* I was introduced to ololiuqui by Mr. Leslie LeCron during a visit to Los Angeles in which he showed me Taylor's (22) article where he compares it with the peyote. Mr. LeCron discovered that seeds of *Rivea corymbosa* could be obtained from Dr. I. D. Clement, Director of the Atkins Gardens and Research Laboratory of Harvard University. I am indebted to Dr. Clement for sending me a supply of the seeds which would otherwise have been very difficult to obtain. It is reassuring for the investigator to know that the substances with which he is experimenting have been collected by skilled scientists who exercise meticulous care, for medical and pharmacological investigators have very often suffered from improper or imperfect botanical determination.

It is now nearly sixty years since Weir Mitchell (8) and Havelock Ellis (2) published their classical papers on the peyote. In the last half century, many investigators have worked with peyote, and especially with mescalin, one of its eight alkaloids, whose chemical formula has been known for many years. Some attention has also been given to hashish (12), as a mixed preparation of the Indian hemp (*Cannabis indica*) is called in North Africa, but there is still much uncertainty about its active principle. In the last decade, two synthetic compounds, lysergic acid (5) and adrenochrome (4) have been discovered to have qualities which allow them to be placed with the naturally occurring hallucinogens. Lysergic acid has been extensively investigated by psychological, physiological, and pharmacological means. Similar work is being started with adrenochrome. In the meanwhile, there are still a number of unusual substances in the world which have received scant attention from investigators, although each one sounds intriguing enough to warrant at least a glance. This paper is a brief glance at one of them.

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* The original title for this paper was "Ololiuqui: Flower-her-Mother". Dr. R. E. Schultes forbade the use of this, writing "*do not use it in your title*". He pointed out that "Flower-her-Mother" is an exact translation of the Mazatec word na-so-le-na designating the seeds of *Rivea corymbosa*. It would be meaningless to attach it to ololiuqui, an Aztec word. Nevertheless so that readers who enjoy a lovely word should not be deprived of its euphony, I have begged a few lines for "Flower-her-Mother."

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## OTHER REPUTED HALLUCINOGENS

Why should we bother with the odd properties of queer drugs from strange places? Apart from an innate curiosity which has drawn men to them since the earliest times, there are other reasons. The changes in perception, affect, thinking, and sometimes posture, which follow the ingestion of these substances, have, it has recently been observed (9) much in common with the acute phases of schizophrenia. It is therefore possible that a wider knowledge of these hallucinogens, as they have been inelegantly termed (4), might lead to a better understanding of the massive psychosis which fills one out of every five hospital beds in the world. So grievous is the burden in suffering and expense of this illness, and so slender our understanding of it, that we cannot neglect approaching it by routes that may at first seem circuitous.

I know of at least four substances, said to be hallucinogenic, of which we have little systematic information. These are:

Harmine, which is derived from the Syrian rue. This is apparently synonymous with banisterine, and yageine, from Caapi (*Banisteriopsis spp*.). The same substance was given the intriguing name of telepathine by Fisher-Cardenas (13) in 1923. While Gunn (7) has made some important studies of its pharmacology, very little seems to be known about its psychological effects. Even less is known about ibogaine derived from the iboga bean which grows in Gaboon. Albert Schweitzer (18), in a recent publication, refers briefly to its psychological properties, but I have been unable to trace any other information so far. Amanita muscaria, a remarkable fungus from a deadly family, has been used extensively in Siberia and is notable for the great potency of its active principle which can survive several passages through the human body: It is excreted in the urine and some Siberian tribes have developed from this an economic, but to our taste unaesthetic, form of conviviality.

Cohoba, a narcotic snuff used in Haiti for necromancy, was described by Ramón Pané who sailed with Columbus in 1496. This snuff was later confused with tobacco. It is derived from a leguminous plant called *Piptadenia peregrina*, and its active principle is believed to be bufotenine (21). I have not discovered a modern account of its psychological effects.

## RIVEA CORYMBOSA

Schultes's (16) valuable monograph provides much information in a compact form about the history and identification of ololiuqui. The conquistadors and their inquisitorial companions were displeased when the Indians, whose countries they had ravaged, clung to some of their ancient customs in spite of rigorous persuasion to abandon them. Victors are always readier to force the vanquished to abandon old habits which are distasteful to the new order than to deal with their own shortcomings. The conquistadors were no exception to this melancholy rule. In spite of Spanish persecution, which was as cruel as it was pious, the Indians continued to revere their sacred plants. Indeed peyote, far from losing its aura of divinity, has in recent years become very closely associated with Christianity (11), and has more devotees now than it ever had in its history. Its cult has spread widely over this continent to Indians who have never used it before.

Ololiuqui has not received the same attention from psychiatrists as peyote, and the reason for this is clear from the data in Schultes's monograph. Until his work was published in 1941, there was an unresolved dispute among botanists as to the plant from which the inconspicuous seeds, which the Indians chewed so persistently, derived. Safford (14) maintained, in the face of much evidence to the contrary, that ololiuqui was the seed of *Datura meteloides*, and such was his eminence in the ethno-botanical field that many followed him. Schultes, however, has now established that ololiuqui is the seed of *Rivea corymbosa*, a large, scandent, twining, woody vine of the *Convolvulaceae* (Morning Glory family). It is the only species of the *Rivea* known in the New World, and is found in the West Indies, South America, Central America, and Florida, growing wild.

## SUBSTANCES PRESENT

Until 1937, when the late Professor Santesson (15) of Stockholm discovered an active narcotic principle in the seeds of *Rivea corymbosa*, no intoxicating substances were known to occur in the *Convolvulaceae*. Santesson was unable to identify this narcotic chemically but concluded that it was an alkaloid combined with a sugar. He did not isolate this alkaloid, so that its chemical formula is unknown.

## PSYCHOLOGICAL EFFECTS OF OLOLIUQUI

Schultes has drawn his information on the psycho-physiological effects of ololiuqui from many sources, starting with Spanish conquistadors and ending with modern investigators and reports of Indian ololiuqui users. This is the least satisfactory aspect of his fine monograph, and it is hardly fair to blame him for shortcomings which arise because his interest centred in botanical and not in psychological matters.

Schultes discusses only two experiments on human subjects, and since neither of these was in any way affected no further clues became available from their work. A Dr. Marsh of the U.S. Agricultural Service "obtained negative results when he experimented with the seeds of *Rivea corymbosa*, and Reko although he had been warned that five or six seeds would produce an intoxication, ate a handful without noticeable effect". Santesson was much puzzled by this immunity and indulged in some speculation about "Racial differences in susceptibility to intoxication" to account for it. While there are differences in susceptibility to all sorts of intoxication, and doubtless racial characteristics play some part in this, there seems to be a simpler explanation for Reko's immunity. The impetuous man had a whole handful to get down and unless I am much mistaken he swallowed them whole. The seeds are small, round and very hard skinned. It requires a determined crunching to smash them with the teeth and unless they are broken up I believe they pass unchanged through the gut. Clement (1) has suggested that the narcotic content of different plants can vary greatly.

Schultes was not able to witness a ceremony in which ololiuqui was being used, nor could he, in the field, partake of the narcotic. Nevertheless it was being used by the Mazatecs as late as 1939 for medicinal and divinatory purposes. I found that the gravest shortcoming was that I was never quite certain whether human or animal experiments were being described. Schultes refers to Santesson's description of what he calls "halbnarcose" and Reko's (16) term "hypnotisch-somnambulistisch". Schultes (17) opines that Santesson's work refers solely to frogs and mice, and tells me that Reko informed him that his account of the intoxication was based chiefly on Indian reports.

However, it seems fairly clear that the Indians, apart from the curative properties which they ascribed to it, also valued it for its use in divination and magic which resembled that of peyote (even though the two drugs are not found in contiguous areas). There seems to have been one interesting difference, for while the peyotist enjoys his transcendental experience in company, the ololiuqui-taker is said to prefer to be alone. A further difference is that most accounts seem to agree that the effects of ololiuqui last only about three hours, which is less than those of peyote. The Spaniards are full of references to witchcraft and devilry, but much of their evidence is coloured by prejudice. Hallucinations and visions are mentioned often but without very much precise description.

Dr. Clement (1) in a personal communication tells me that he has been unable to discover any evidence that it has ever been used as a narcotic in Cuba. Like many other plants, it has a reputation as an abortifacient, though there is no information about its efficiency in this respect. There is some evidence that ololiuqui honey, which is of a very excellent quality, has a somnorific effect.

## DOSAGE

The investigator of any new drug is always glad to have some hint about the amount needed to produce its characteristic effect; the more precise this information, the better. When investigating something whose characteristic effects are said to be psychological, and in which therefore the value of experimental animals is small, it is very hard to determine a suitable dose. The synthetic hallucinogens are easier to work with than the naturally occurring ones, because we know fairly accurately the amount of mescalin or lysergic acid required to produce a model psychosis. We also know that only one substance is responsible. With peyote, we are dealing not only with a mixture of alkaloids, but in addition, the relative concentrations of the eight alkaloids can vary. The directions for taking the comparatively well-known peyote show great differences, so that it is hardly surprising that the information about ololiuqui is likewise deficient.

The natural unwillingness of the Indians to disclose their religious secrets to strangers has been greatly increased by the zeal of generations of Spanish busybodies. Serna (19) gives us a vivid description of the reticence of the Indians and the attitude of the Spaniards. "These seeds . . . are held in great veneration . . . They place offerings to the seeds . . . in secret places so that the offerings cannot be found if a search be made. They also place these seeds among the idols of their ancestors . . . The natives do these things with so much respect that when some transgressor of the law who has the seeds in his possession is arrested and is asked for the paraphernalia which are used in taking ololiuqui . . . or for the seeds themselves, he denies vehemently that he knows anything about the practices. The natives do this not so much because of fear of the law as because of the veneration in which they hold the seed ololiuqui. They do not wish to offend ololiuqui with demonstrations before the judges of the use of the seeds and with public destruction of the seed by burning."

According to Schultes it seems that at least three groups of Indians told investigators that they commonly took thirteen seeds. One of these groups claimed that their reason for doing this is because thirteen was the sacred number that represents Jesus Christ and his apostles at the Last Supper. The seeds are taken in water or with an alcoholic drink such as pulque, mescal (a drink not to be confused with the alkaloid of the peyote), aquardiente, or tepache.

I therefore expected that, if anything happened, thirteen seeds would be enough to produce in a short time dizziness or giddiness followed by lassitude, increasing drowsiness and finally a stuporous state in which visual hallucinations would occur, and I would be only dimly aware of what was going on around me. The evidence suggested that this would last about three hours, but I was not at all clear how I might expect to feel after the stage which has been so oddly termed "somnambulistic narcosis" had worn off.

I had a little information from Mr. L. LeCron and Mr. Aldous Huxley, who took six seeds in February, 1954, without any very clear effect. I later discovered that Mrs. Huxley, on a similar dose, had some delightful visions depicting some new adventure in the life of Wu-Cheng-Ens' (23) heroic and archetypal ape, Monkey. I did not however know of this until after I had taken ololiuqui myself.

## THE EXPERIMENTER, HIS SURROUNDINGS AND THE SEEDS

I weigh about 170 pounds and am 5 feet 9½ inches. I am aged 36 and enjoy good health. I have never suffered from jaundice (4). I am experienced in the model psychoses, having taken mescalin on one occasion and watched others take it. I have taken part in many lysergic acid experiments, although I have not yet ingested it myself. I have taken adrenochrome on three occasions. I can therefore claim some degree of sophistication in these matters. This has the advantage that such a trained observer may be alert to subtle changes which others might ignore and the disadvantage that he might be suggestible and report small changes attributable simply to heightened expectation. There is no easy way out of this dilemma, but in a preliminary trial it is not very important, although in a larger experiment it would have to be guarded against. A full evaluation of a new hallucinogen is, as I have pointed out elsewhere (10), a major enterprise calling for the co-operation and co-ordination of many disciplines. Stefaniuk (20) has shown how complex are the experiential and behavioural changes with which we have to be prepared to deal. I know of no satisfactory study of such an evaluation, or even any discussion of the methods that would be most helpful.

The seeds of *Rivea corymbosa* are about the size, hardness, and colour of a small sweet pea. Technically they are described thus, "being bacchate, dry and indehiscent with only one seed". They are hard enough to need grinding with the molar teeth. Those with dentures should use a hammer or a pestle and mortar. With the help of Mr. D. Sheldon and Mr. Doisey, of the Saskatchewan Hospital, Weyburn, I have devised a tubular steel pestle and mortar with a detachable base which reduces the effort required to smash the seeds and eliminates danger to teeth and dentures. I would be glad to describe it to other experimenters.

The seeds have a bitter taste like lupin or wild bean seed. My sample was not in the least peppery and could not possibly be described in Hernandez's (3) words of 1651 as having "a sharp taste and is very hot". It does not in the least resemble the burning taste of chili, with which, as a curry eater, I am familiar, although Reko states that its Mixtec name yucu-yaha, meaning chili plant, refers to its hot taste. Chewing large numbers of seeds is tedious and they leave a slightly nauseating after-taste in the mouth.

The first and second experiments were done in my own home, alone except for my little daughter who was going to bed when the seeds were taken. My excuse for this slovenly procedure was a scepticism about the potency of ololiuqui fostered by reading Dr. Marsh's experiment. My wife, who has done a good deal of work in this field, and my sister, who is a registered nurse, were present during the third experiment. I had no verbal means of recording for two of the first three experiments, and when I had a dictaphone, for reasons that are not clear, I did not use it. I did however take notes with a greater or lesser degree of assiduity.

In the fourth experiment, which was again conducted in my home, my psychologist colleague Mr. Ben Stefaniuk was present. He took down most of our conversation on tape, and also made a series of notes such as he has used in our lysergic acid experiments, indicating changes in behaviour and the time at which these occurred. The number of seeds taken were 14, 26, 60 and 100 in that order. For the first three experiments, they were chewed and washed down with iced water. In the fourth they were smashed with a hammer and then ground to a fine flour in a glass pestle and mortar. This fine flour was placed on the tongue with a teaspoon and swallowed with iced water.

## The Experiments

### *One*

At 6.15 p.m. on Friday, 20 February, 1954, I chewed up fourteen of the seeds. I felt that this number was less of a challenge to the fates than the thirteen favoured by the Indians. I noted "I am alone with little H. A definitely unexperimental atmosphere—am strongly of the opinion that nothing will happen."

6.30 p.m. One of those curious things that might be suggestion: an extraordinary clarity of objects. "The tennis ball, white and furry on the tomato coloured carpet and a little cluster of glass marbles some eighteen inches away from it. All seem to be related to one another and each seems to have special significance" . . . "Irritability is noticeable especially when disturbed" . . . "My gaze is caught by the polish on the willow shoots, the greenness of a leaf, the furriness of a cactus. This could be heightened awareness due to heightened expectation."

6.45 p.m. I ate a fair supper although not keen to do so. Nothing more happened. I read quietly all evening. I did not record another note although I had meant to do so.

### *Two*

Exactly a week later I took 26 seeds in similar circumstances and had a very similar experience. Although I had a dictaphone with me and had brought it a considerable distance for this express purpose, I failed to record or keep notes of any sort. This could be ascribed either to incompetence or to the effects of ololiuqui. I prefer the latter explanation, because I am quite aware of the requirements of this sort of research and am usually a fluent writer.

### *Three*

7 March, 1954. At 12.30 p.m. I chewed sixty seeds and washed them down with water. I took notes most of the time. At 1.0 p.m. I had lunch, which was tasteless, though I ate some of the same food later with enjoyment. At 1.30 p.m. I noted this—"A slight headache, vague, unlocalized. A great effort to write, easier just to sit. People irritate; things fascinate: the texture of wood: the almost metallic gold centre of an African violet. Mildly nauseated. The little warm dog on my lap the only contact."

2.0 p.m. "Very indolent and irritable, curious sense of distance—noise uncomfortable—pup consolingly real. Children coming in a very real threat. H. (my 4 year old daughter) wants to come close to me and the dog. Find this most disturbing, say 'Go away, go away.'" "Lethargic, irritable, scarcely bother to write."

2.10 p.m. "On closing my eyes hypnagogic phenomena, much vivider than usual at this time of day." (Normally on eye closing I do not have hypnagogic phenomena unless very tired.) "I have no wish to explain or communicate. The little dog alone remains in contact, demanding nothing, not even understanding."

2.20 p.m. "Eyes closed. Curious patterns. First blackness so deep that my hair stood on end. Then a beige-grey ceramic design, with silver stippled patterns, an abstract design of an ibex. Do I mean ibex—a horned deer—yes ibex, not ibis the bird."

2.40 p.m. "A very difficult state to describe. Every action seems discreet and uncertain. Very difficult to make up one's mind to do anything." J. my wife read my notes, "J. is reading this and I am conscious of this in an entirely detached way, as if she were reading my diaries post-mortem. Also feel rather silly as I write this down, though I know it will worry her and she is worried." "Objects seemed to have an extraordinary solidity and dimensionality." "That scarlet piece of wood on the brown carpet, it is so intensely bright that the colour seems to sink into the carpet." "A curious idea that I am writing and wasn't getting any forrader or anything down—a sort of nightmare self erasing writing." "One is bewildered by the wonder of each single object."

3.30 p.m. "Irritable apathy is the keynote. Too apathetic to call out. Too irritable to dare to do so. On and on and on." "Eyeball pressure does change the hypnagogic images temporarily but they return when the pressure is released. How bright the light—how shadowy people, even H. Even their voices seem dull and meaningless. The little dog is deliciously alive. N.B. shouldn't psychotic people have pets? Wouldn't they be more helpful than humans? Probably. Why? Because they are not self conscious, hardly selves at all. Maybe this is why we can't help each other because we are literally selfish. Self gets in the way, even with H. but not with the little dog. A cat too is so completely cattish, that no self, no human self intervenes. Animals are alive but undemanding."* "Bodily sensations less than mescalin, some epigastric burning, some tingling in face and hands, slight headache, not much else." "This is a waking dream.† So little changed, but enough. The cat might be artificial, a mechanical cat, but little Mesca (dog) is clearly alive." "Looking at oneself in the mirror. How can I be sure that it is me; perhaps it isn't." "Once I start writing I keep going automatically, my attention is fixed on the writing. It is the same with everything. I stick in a groove. If I got angry would I stick in it? I don't know, I'd better not try."

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* As Walt Whitman put it in *Song of Myself*

I think I could turn and live with animals, they are so placid and self contained.
I stand and look at them sometimes half the day long.
They do not sweat and whine about their condition,
They do not lie awake in the dark and weep for their sins,
They do not make me sick discussing their duty to God
Not one is dissatisfied, not one is demented with the mania of owning things.
Not one kneels to another, nor to his kind that lived thousands of years ago.
Not one is respectable and industrious over the whole earth
So they show their relations to me, and I accept them.
They bring me tokens of myself, they evince them plainly in their possession.

† Somnabulistic narcosis although a clumsy term would not be an entirely inappropriate description.

6.0 p.m. "This is very curious stuff. I have been lying on my bed asleep, but not really asleep for the last 2½ hours. I have slept a bit and have been profoundly tired, yet acutely aware of everything that was going on. A sort of paralysis of the will; it is an immense effort to do anything yet when I do it, I can." . . . "Although not keen to be near people I feel it when they go away." . . . "In this dose this is not a hallucinogen to any great extent. In larger doses it may be so. It produces stupefaction without disorientation or the motor effects of alcohol. One is irritable, stuporous, apathetic, but not very uninhibited."

7.0 p.m. Within an hour of eating a sugary meal and drinking tea I noted, "Now very much more normal, very alert, and very aware of what is going on. It looks as if this stuff acts on different centres at different times."

8.0 p.m. I eat a hearty meal. "It seems to have worn off leaving elation and clarity without tension. It is the reverse way round from Benzedrine."

That night I went to bed about midnight and slept fairly well, though I had some hypnagogic phenomena before falling off to sleep. When I awoke next day I was slightly tense and had a mild frontal headache—nothing like a hangover—my tongue was clean and moist.

### *Four*

This experiment was again conducted in my home on the 21 March, 1954. It was fully recorded on tape and where I quote it is from a transcript of this record or from the few notes which I made. My colleague Mr. Ben Stefaniuk was present as an observer. At 12.10 p.m. I took 100 seeds reduced to a powder as I have already described. The symptoms, which started within twenty minutes of swallowing the powder, followed the same general pattern as the third experiment, and consisted of apathy, anergia, withdrawal, some sharpening of visual perception, and an increase in hypnagogic visions when the eyes were closed.

The apathy extended to the experiment, showing itself in a lack of interest. For instance when I was pressed to talk more I said, "Yes this is an experiment but I don't attach much importance to it." My interest in people lessened. "It is difficult to be interested in them, they shift around so much." I had feelings of weakness and doubted whether I could hold the microphone, but this weakness was not accompanied by clumsiness as in alcoholic excess. "I feel extremely steady but very weak."

At 1.34 p.m. a curious thing happened. I raised my hand above my head and couldn't get it down. No urging or verbal pressure by my colleague made any difference, neither did voluntary effort on my part. "I can't. It's stuck. That is strange, an unpleasant feeling." Eventually I pulled it down with the other hand.

I had no slurring of speech and at about 2.30 p.m. repeated "Popocatepetl" several times and very clearly. It was not easy to judge time and I had to work it out. "I'm not disorientated in time but it is extremely difficult to tell where in time I am." I referred frequently to my tiredness. Towards 3.30 p.m. I began to feel hungry, having had no inclination for food before that, but I was too lethargic to do anything about it. "It is quite strange how I fluctuate from feeling full of energy to feeling completely done in." About this time my companion asked "What about the seriousness of the experiment?" I replied, "It is there intellectually but I don't feel about it—intellectually I am well aware that this is an interesting thing, but the fact is I don't feel interested in it. I really don't feel that I have the energy to be interested you know. And this doesn't quite fit into anything. It's not derealization or depersonalization. Those are almost meaningless words for certain states certain people believe they have observed in other people. But these things are not exactly applicable to me. It's something you can apply to someone else but not to yourself. This is not the feeling of being an 'it' at all. It is simply a feeling of complete detachment from the situation and being an observer; not being a thing."

Pressed to explain myself by Mr. Stefaniuk I continued: "I was feeling that I really hadn't the energy either intellectual or physical to discuss what was happening, and though there were these perceptual changes which were not unlike the early stages of mescal or adrenochrome, the main thing was this extraordinary lack of energy*—an extreme unwillingness to do anything at all." This apathy and anergia could, most of the time, be overcome by an intense effort, but at the height of the experience voluntary effort made little difference.

From 4.0–4.30 p.m. I found that it was increasingly possible to exert sufficient effort to dispel the lethargy. "You can overcome apathy if it lasts a short time, but if it lasts a long time you just can't do anything."

About 5.0 p.m. I went for a drive and was interested to discover that I had none of the time and distance disturbances that I had had with adrenochrome. I ate a substantial meal.

By 6.0 p.m. I felt recovered and was active, interested and continued in this state for many hours. I noted, "Apathy, lack of energy, seems to be the keynote with only a little disturbance of perception . . . Apathy (no mood) is clearly differentiated from depression (low mood) . . . The lack of angst differentiates this from LSD or mescal."

11.15 p.m. after driving my friend home—"Still a depth and brightness in things such as they have on a May morning when you are twenty-one. A newness, freshness as if everything had had a spring shower". . . "Silence seems deeper, noises seem crisper. Oddly this was present in the apathy and is still present in this pleasant alertness without tension and without foreboding. It is very different from the touch-me-not feeling after mescalin or the bruised blunting after alcohol."

I went to bed about midnight but did not go to sleep immediately but lay relaxed and wakeful, letting associations come and making notes in the dark which weeks later are legible and seem quite sensible. At about 1.0 a.m. our little daughter awoke with a cough. Normally I would have found this irritating and would have been disgruntled. I noted, "I was cheerful, relaxed and alert. The lack of the caffeine or benzedrine tension is remarkable."

Next day I awoke at 7.0 a.m. I had a slight dryness of the mouth—no hangover. I was, it seemed, hypo-irritable yet hyper-alert. Doors banging, etc. did not in the least disturb me even though it was Monday morning. During the day's work, I think that I was more active and less touchy than I would expect after such exertion and a poor night's sleep.

### PSYCHOLOGIST'S COMMENTS

Mr. Ben Stefaniuk was kind enough to make the following comments on the fourth experiment:

"The most apparent and constant element in the experiment was that Dr. Osmond, who usually is a very energetic and talkative person, became extremely lethargic and uncommunicative. I tried to interest him in the importance of the experiment at various intervals, but, very much to my surprise, he claimed that it wasn't too important and the recording of the experiment could wait. This is an amazing reaction because, from previous discussion, I knew him to be extremely interested in the outcome of this experiment. There was nothing bizarre in either his behaviour or his verbal productions; it was not similar to most LSD reactions. His type of uncommunicativeness was displayed in many qualifying instances by one of my female volunteers for LSD. The main changes, I feel, were lethargy, alternating with periods of restlessness, a similar type of loss in interests and the extreme slowing down of verbalization."

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* In an experiment with adrenochrome (4) I had the curious experience that I was a thing, not a person.

## Discussion

I believe that this is the first series of experiments with ololiuqui, said by Safford (14) to be "the chief narcotic of the Aztecs", conducted solely for the purpose of psychological investigation. Previously, apart from Marsh and Reko (16), who heroically swallowed a "handful" of the seeds, all accounts of the effect of ololiuqui seem to have been obtained from the Indians. The descriptions recorded by the conquistadors and their descendants were distorted by the hatred which they felt for the defeated. Later enquiries by scientists were impeded by lack of psychological knowledge which would have enabled them to make the most of their informants, who were no doubt becoming increasingly wary of divulging their secrets. In support of my contention that neither Marsh nor Reko chewed the seeds which they swallowed is the fact that Reko, in 1934, still repeats Hernandez's (13) assertions of 1651 that ololiuqui "has a sharp taste and is very hot". Reko states that the Mixtecs give it the same name as the chili plant, yuca-yaha. My sample of ololiuqui had only a slightly bitter taste, and bore not the slightest resemblance to chili, whose pungency could not possibly be overlooked when placed in powdered form on the tongue. Can it be that a reputation for such pepperiness would discourage the curious? Or could it be that the seeds were gathered unripe or less ripe in one case than the other?

Nevertheless, apart from this and the number of seeds needed, the information gathered from the Indians seems to have been accurate, although incomplete. Thirteen seeds, in spite of their sacred significance, had very little effect on me. There may be more subtle explanations, but I suggest that red men, from bitter experience, have found it prudent to mislead white men, lest they once more prohibit the sacred seed and persecute its devotees.

This preliminary exploration suggests that ololiuqui differs from mescalin, lysergic acid and adrenochrome. In doses of 60–100 seeds it produces marked anergia and irritable apathy, combined with alert thought processes and increased hypnagogic phenomena. This is odd; even odder is the rapid onset, short duration, and lack of hangover, followed by alert wakefulness without tension. This alert wakefulness is noteworthy for an unusual placidity combined with a capacity for constructive action when required. I could drive a car so that a critical passenger was not disturbed.

The "paralysis of the will", which occurred with the apathy and anergia, is not unlike the complaints of some people who are labelled schizophrenic. These unlucky folk complain about their lack of energy and are looked upon as being "bizarrely hypochondriacal". They get very little understanding or attention, usually. When they are forced to overcome their anergia, they often become irritable and sometimes their behaviour seems to be impulsive. I know that in one experiment I made what was intended to be a gentle push at my little daughter to fend her away and knocked her flat. The effort once made resulted in action that did not seem to be fully controlled. At the height of the experience so much effort was needed to do even the smallest thing that there was a temptation to remain totally immobile. Even in this immobility I was alert and aware what was going on most of the time. Most psychiatrists have seen patients who could be described in this way.

Most writers agree that the Indians reverence ololiuqui for its use in magic, divination, and as a vision maker. Taylor (22), quoting an old authority writes: "They consult it as an oracle in order to learn many things . . . especially those things which are beyond the power of the mind to penetrate." May it not be that the Indians take it as much for the astonishing, detached, serene well-being and mental clarity combined with a capacity for action without anxiety which follows the apathy, as for the visions, etc.? Surely this remarkable state would be an excellent jumping-off place for starting that "active contemplation" so much sought by explorers of the soul, and so hard to achieve?

Like most writers whose special province is not psychology, Schultes is vague about "hallucinations". I did not experience any, though I had some heightening of visual perception with the eyes open and some increase of hypnagogic visions when they were closed.

My response to ololiuqui is almost the reverse of that to amphetamine, which causes me to have a short period of tense elation and over-activity, followed by black depression. If other experimenters also find this happens, there would be a very strong case for isolating the active principle and comparing its spatial formula and effect on cerebral enzyme systems with amphetamine.

The comfort which I derived from the close presence of the little dog requires some thought. While we have made a cult of pet animals in the West, there seem to have been few studies of the relationships which develop between animals and humans. This is often dismissed as being a substitute for another relationship—a human one. In my view this is superficial and misleading. The relationship between man and dog has developed over tens of thousands of years and seems to be based on a deeper level of understanding than words. Perhaps then, when words fail us, this is why dogs can be so comforting.

A few experiments on one subject can tell us very little, but this seems to be another instrument which may allow us to ask questions which will help us towards a greater understanding of ourselves.

Many questions spring to mind. What is the active principle of the elusive ololiuqui? How and where does it act? In what other ways will people respond to it? But future investigators would be glad if a few quite mundane questions were answered first. What exactly are the local anaesthetic properties that Schultes mentions? A full pharmacological investigation would be very welcome.

## SUMMARY

I have reported four experiments with ololiuqui (*Rivea corymbosa*), a narcotic used by the Aztecs. This is the first time, to my knowledge, that the psychological effects of the seeds of this plant have been discussed in a medical journal. The active substance or substances present are not known. I found that I required about six times the thirteen seeds which Schultes reported as the dose commonly used by the Indians, though he emphasizes that dosage seems to vary. The accounts gleaned from the Indians give only a partial description of the experience produced by ololiuqui. This consists of apathy and anergia combined with some degree of heightened visual perception and an increase in hypnagogic phenomena. There is no confusion, indeed one is very acutely aware, though time perception is altered.

After about four hours this is replaced by a period of alert, calm, relaxed well-being lasting many hours. A condition which I have not seen described before and which is very pleasant.

I think ololiuqui requires further and fuller study, and I hope that this small reconnaissance will arouse enough interest to encourage larger and better equipped expeditions into this strange territory.

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# ADRENOCHROME AS THE CAUSE OF SCHIZOPHRENIA: INVESTIGATION OF SOME DEDUCTIONS FROM THIS HYPOTHESIS

By

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## THE WORKING HYPOTHESIS

OSMOND and Smythies (1952) have given reasons for reviving the view originally put forward by Bleuler (1950) that schizophrenia is essentially a disorder of metabolism, and have suggested that some substance chemically related to mescaline might be the causative agent. Hoffer, Osmond and Smythies (1954) have begun an investigation of this hypothesis and have found that adrenochrome, an oxidation product of adrenaline which is probably a normal intermediate metabolite, has active hallucinogenic properties. These authors do not regard adrenochrome as being unquestionably the toxic agent in schizophrenia, but suggest that it or some closely related substance, having the indole ring and derived from adrenaline, is involved. They also advance the opinion that the metabolic fault consists of an overproduction of adrenochrome or similar substances. Such a view necessarily implies either overproduction of adrenaline or a blocking of one or more of the paths of adrenaline detoxification in the body which do not lead through adrenochrome. As adrenaline is derived from tyrosine the hypothesis is essentially one of abnormal tyrosine metabolism. From this hypothesis certain deductions can be made.

## DEDUCTIONS

A. *Abnormal pigmentation.* Tyrosine (which may be ingested as such or derived in the body from phenylalanine) is also a precursor of the normal biochrome melanin, one metabolic path leading through adrenaline and adrenochrome. It is to be expected that any interference with this chain of reactions will produce an abnormality of pigmentation (compare, for example, Addison's disease, phenylpyruvic oligophrenia, etc.). One such abnormality, increased formation of melanin and its deposition in the skin, has been described in schizophrenia (Loehner, 1938), and Hoskins (1946) is of the opinion that disorder of the adreno-sympathetic system, which is involved in pathological pigmentation, is one of the most constant features of this disease. Clearly the type of pigment anomaly, increase or decrease, will depend on the point of interference with the metabolic path. In phenylpyruvic oligophrenia the break occurs in the first stage, the conversion of phenylalanine to tyrosine, so that it is to be expected that shortage of pigment will be found, and this is well known to be the case. In the present disease the abnormality is assumed to consist of an excess, either by overproduction or accumulation, of adrenochrome. As adrenochrome is a very unstable substance and is oxidized to melanin at physiological pH without enzymatic aid, it is to be expected that an overproduction of melanin will result, and a preponderance of the dark type of individual be found in schizophrenics.

B. *Negative association with the allergic states.* It has been shown by Lucy (1954) that schizophrenics have a greatly increased tolerance to histamine.

Adrenaline is one of the most satisfactory forms of treatment of the acute allergic states, i.e. acute histamine poisoning. In experimental anaphylaxis, i.e. acute histamine poisoning, one of the findings is melanuria (Haden and Orr, 1924), suggesting that excess adrenaline is being produced in an attempt to combat the effects of the histamine, and eventually proceeding to melanin *viâ* adrenochrome. It has been shown that concentrations of the order of $10^{-6}$ of adrenochrome have an antihistamine action (Hutcheon, 1955), so that the assumption that abnormally large amounts of adrenochrome are accumulating could explain this increased histamine tolerance in the schizophrenic subject. From this it follows that there should be a greatly reduced incidence of the allergic states in a population of schizophrenics.

C. *Ascorbic acid metabolism.* It has been shown that ascorbic acid prevents the oxidation of adrenaline to adrenalone, the immediate precursor of adrenochrome, in surviving slices of adrenal gland (Heard and Welch, 1935). It is well known that in certain cases of Addison's disease the pigmentation of the skin is much lessened by administration of large amounts of ascorbic acid. It has been shown, *in vitro*, that concentrations of sodium chloride below physiological limits accelerate the destruction of ascorbic acid and produce increased formation of melanin from both tyrosine and adrenaline (Lea, 1945). The occurrence of a schizoid state in Addisonian patients is well known. From these facts it seems that an attempt to treat schizophrenia with sodium chloride and ascorbic acid would be justifiable.

D. *Tyrosine metabolism.* Any attempt to treat schizophrenia by interfering with the amino-acid intake appears, at first, to be a highly speculative and possibly dangerous undertaking. However, Bickel, Gerrard and Hickmans (1953) described such remarkable clinical improvement in a case of phenylpyruvic oligophrenia following carefully controlled reduction of phenylalanine intake that experiments in treatment of schizophrenia along similar lines, i.e. reduction of tyrosine and phenylalanine intake to the physiological minimum, would seem to be justified.

E. *Abnormal substances in the urine of schizophrenics.* By analogy with the finding of melanuria in experimental anaphylaxis it might be expected that this or some similar urinary abnormality would occur in schizophrenics. Churchman (1924) reported five instances of melanuria in cases of unspecified mental disease. No further reference to this work has been found in the literature, but it does seem probable that some abnormal indole body, or excess of the normal indole derivatives, might be present in the urine of schizophrenics.

It has been found possible to investigate two of these deductions, viz. abnormal pigmentation and negative association with allergic states.

## Material and Methods

A series of 1,008 cases of schizophrenia occurring in men serving in the forces during the recent war has been investigated. The cases used were not entirely free from selection as (1) they were limited to the male sex, (2) they were of the standard of physical and mental fitness necessary for service in the forces, (3) they were limited to the age groups of serving men, and (4) they were diagnosed during the years 1943–44. This last restriction was imposed in order that ample time should have elapsed since the first diagnosis to allow of its full confirmation. It must be pointed out that factors (1), (2) and (3) above prevent direct comparison between this series and those drawn from the general population.

The eye and hair colours of these men were recorded by recruiting boards, together with the age at the date of the observations. Such records cannot have a great degree of accuracy, but reasons have been given (Lea, 1955) for regarding them as adequate for the present purpose. These colours have been compared with those of a control series of 5,127 cases of injury, previously prepared for such a purpose (Lea, 1952) and subjected to the selection factors (1), (2) and (3) as in the schizophrenic series. Eye colours have been recorded as blue or non-blue, hair colours as fair or dark. In addition the data have been classified according to the scheme devised by MacConaill (1941–42), viz. blond=blue eyes and fair hair, dark=dark eyes and dark hair, glaucope=blue eyes and dark hair, cyanope=dark eyes and fair hair. For the purposes of this investigation blue, grey-blue and grey eyes have been grouped together as blue, all others as non-blue. Fair, blond, light brown and flaxen hair have been grouped as fair, all other colours including red as not-fair (=dark).

For the investigation of the allergic states the full case histories, including hospital and other records since discharge from the forces, of a random series of 500 of these schizophrenics were searched for evidence of any form of allergy. This was also done in a control series of 500 cases of head injury. Head injuries were chosen for the control series because the case notes in this type of injury went more fully into details of past history, family history, etc., because of the possibility of post-traumatic personality changes, than did those of other types of injury. Even so it is very probable that the incidence of allergy in these head injury cases as recorded here was an understatement, for their case histories as a whole were not as detailed as those of the schizophrenics. It must also be noted that the incidence of the allergic states in these cases gave no indication of the true incidence of these conditions in the general male population of the same age groups. This was because two important selective factors operated, (1) men with obvious allergy would not be accepted for the forces, and (2) those with severe allergic conditions which became manifest after enlistment would be discharged for this reason. The incidence here was of the mild allergic conditions, overshadowed in immediate importance by either the head injury or the mental condition. It is to be noted that these selective factors apply to both the schizophrenic and head injury series and therefore cannot be regarded as having affected the findings of this investigation.

## RESULTS

The eye and hair colours and the MacConaill types of 1,008 cases of schizophrenia, together with those of 5,127 cases of injury, are given in Table I. It will be seen that the percentages for all ages differed very little in the two series, and the values of chi$^2$ for comparison of eyes, hair and MacConaill types were 0·300, 2·557 and 4·199, giving values for P of 0·5–0·7, 0·1–0·2 and 0·2–0·3, all non-significant results. However, it is known that the proportions of these different colour types vary with age, so the data were subdivided into the age groups 15–19, 20–24 and 25 years and over (further division was not possible because of the smallness of the numbers in the higher age groups). Comparison again produced no significant findings in eye colour, chi$^2$=4·223, P=0·1–0·2, but in hair colour and the MacConaill types some striking differences were found. For hair colour chi$^2$=12·702 which, with 3 degrees of freedom, gave P less than 0·01, and in the MacConaill types chi$^2$= 18·381 which, with 9 degrees of freedom, gave P between 0·02 and 0·05. In hair colour the age group 15–19 years contributed 10·582 to the total of chi$^2$,

TABLE I

*The Eye and Hair Colours of 1,008 Schizophrenics and 5,127 Cases of Injury, in 5-Year Age Groups*

(Figures in brackets are percentages, "age" refers to age at which data were recorded)

| | Age Groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 15–19 | | 20–24 | | 25 and Over | | All Ages | |
| Character | Schizo-phrenics | Injury | Schizo-phrenics | Injury | Schizo-phrenics | Injury | Schizo-phrenics | Injury |
| Blue eyes .. .. | 169 | 907 | 279 | 1,099 | 159 | 1,034 | 607 | 3,040 |
| | (56·5) | (60·8) | (61·6) | (58·9) | (62·1) | (58·4) | (60·2) | (59·3) |
| Non-blue eyes .. | 130 | 585 | 174 | 766 | 97 | 736 | 401 | 2,087 |
| Fair hair .. .. | 58 | 426 | 112 | 420 | 48 | 383 | 218 | 1,229 |
| | (19·4) | (28·6) | (24·7) | (22·5) | (18·8) | (21·6) | (21·6) | (24·0) |
| Dark hair .. | 241 | 1,066 | 341 | 1,445 | 208 | 1,387 | 790 | 3,898 |
| Blond .. .. | 48 | 338 | 91 | 347 | 42 | 292 | 181 | 977 |
| | (16·2) | (22·7) | (20·1) | (18·6) | (16·4) | (16·5) | (18·0) | (19·1) |
| Dark .. .. | 120 | 497 | 153 | 693 | 91 | 645 | 364 | 1,835 |
| Glaucope .. .. | 121 | 569 | 188 | 752 | 117 | 742 | 426 | 2,063 |
| Cyanope .. .. | 10 | 88 | 21 | 73 | 6 | 91 | 37 | 252 |
| Totals in age groups | 299 | 1,492 | 453 | 1,865 | 256 | 1,770 | 1,008 | 5,127 |

this group alone having a value for P of much less than 0·01, and in the MacConaill types the same age group contributed 11·731 to the total of chi$^2$ with a value for P of less than 0·01. In each case the remaining two age groups had non-significant values for P of 0·1–0·2 and 0·05–0·1 respectively.

It is also known that the proportions of the colour types vary in different parts of Great Britain. The data were further subdivided into areas of birthplace, but of these only the London area had figures sufficiently large for statistical comparison. The data for this area are given in Table II. For hair colour in the London area, by age groups, chi$^2$=10·916, P being between 0·01 and 0·02. The age group 15–19 years contributed 9·239 to the total, P for this group being much less than 0·01. Eye colour gave chi$^2$=3·483 with a value for P between 0·3 and 0·5. There were too few in the cyanope group of the MacConaill types for comparison to be made.

TABLE II

*The Eye and Hair Colours of 246 Schizophrenics and 1,054 Cases of Injury Born in the London Area, by Age Groups*

(Figures in brackets are percentages, "age" refers to age at which data were recorded)

| | Age Groups | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 15–19 | | 20–24 | | 25 and Over | | All Ages | |
| Character | Schizo-phrenics | Injury | Schizo-phrenics | Injury | Schizo-phrenics | Injury | Schizo-phrenics | Injury |
| Blue eyes .. .. | 40 | 170 | 58 | 192 | 48 | 220 | 146 | 582 |
| | (56·3) | (59·0) | (57·4) | (52·9) | (64·9) | (54·6) | (59·3) | (55·2) |
| Non-blue eyes .. | 31 | 118 | 43 | 171 | 26 | 183 | 100 | 472 |
| Fair hair .. .. | 12 | 103 | 29 | 97 | 13 | 97 | 54 | 297 |
| | (16·9) | (35·8) | (28·7) | (26·7) | (17·6) | (24·1) | (22·0) | (28·2) |
| Dark hair .. | 59 | 185 | 72 | 266 | 61 | 306 | 192 | 757 |
| Blond .. .. | 10 | 80 | 24 | 79 | 13 | 67 | 47 | 226 |
| | (14·1) | (27·8) | (23·8) | (21·8) | (17·6) | (16·6) | (19·1) | (21·4) |
| Dark .. .. | 29 | 95 | 38 | 153 | 26 | 153 | 93 | 401 |
| Glaucope .. .. | 30 | 90 | 34 | 113 | 35 | 153 | 99 | 356 |
| Cyanope .. .. | 2 | 23 | 5 | 18 | 0 | 30 | 7 | 71 |
| Totals in age groups | 71 | 288 | 101 | 363 | 74 | 403 | 246 | 1,054 |

The incidence of various allergic states in 500 cases of schizophrenia and 500 cases of head injury is given in Table III. (Eczema was only included when

TABLE III

*The Incidence of Allergic Conditions in 500 Cases of Schizophrenia and 500 Cases of Head Injury*

| Allergy | Schizophrenia No. of Cases | Head Injury No. of Cases |
|---|---|---|
| Asthma | 1 | 4 |
| Urticaria | 0 | 2 |
| Eczema | 0 | 7 |
| Henoch's purpura | 0 | 1 |
| Hay fever, rhinitis | 0 | 4 |
| Drug sensitivity | 0 | 4 |
| All types | 1 | 22 |

there was a history of recurrent attacks since childhood and the diagnosis confirmed by a dermatologist.) Difficulties arose as there were no firm grounds for ranking different types of allergy as equal from the point of view of the seriousness of the disease. It could not be held that they represented equal degrees of hypersensitivity, or equal degrees of histamine poisoning, etc. It was also impossible to grade the various types of allergy on the basis of their risk to life, for though it would be generally held that, as an example, asthma is a more serious condition than drug sensitivity, yet the majority of asthmatics have a normal length of life, whereas one of the cases of head injury in the present series had such a near-fatal reaction (severe urticaria, oedema of the glottis, etc., necessitating emergency treatment) to the routine service inoculations that he was provided with a letter of warning to anyone who might have to treat him in the future. It was finally decided that for the present purposes all the various allergic states would have to be ranked equal as cases of undue histamine sensitivity, without regard to the degree of such sensitivity, and the data treated as individuals with allergy as opposed to those without, and the calculations made on that basis.

A further problem was provided by the cases of drug sensitivity. These were confined to the head injury series and consisted of abnormal reactions to penicillin and other antibiotics. The difficulty was due to the fact that all the open head injury cases received sulphonamides, penicillin, etc., as routine treatment, whereas the schizophrenics did not, though many of the latter did have treatment with antibiotics for various reasons. Clearly the risk was not the same in the two series, and it was decided that the cases of drug sensitivity should be omitted from the calculations, though they are shown in Table III for the sake of completeness.

Family history of allergy was also recorded. It was found that in only one schizophrenic, the solitary case with asthma, was there a family history of allergy as compared with seven in the head injury series. These cases were unfortunately too few for statistical treatment. Finally one case of head injury had both asthma and eczema, reducing the number of affected men in this series to 17.

Comparison of the 17 cases of allergy in the head injury series with the one case in the schizophrenic series, using Yate's correction, gave $\text{chi}^2 = 13 \cdot 230$ which, with one degree of freedom, gave a value for P of less than $0 \cdot 001$.

## SUMMARY OF RESULTS

(1) The analysis of the data showed that there was a highly significant excess of dark hair in schizophrenics in the age group 15–19 years, with no significant difference in eye colour, as compared with a series of cases of injury. The deficiency of blonds is probably significant but cannot be said to be definitely so.

(2) There was a highly significant deficiency of individuals with allergic conditions in the schizophrenia series.

(3) For both the excess of dark hair and the deficiency of allergy in the schizophrenics the probability of the observed results being due to chance is approximately 1 in 1,000.

## DISCUSSION

*The excess of dark haired subjects.* (The very important fact that this excess is limited to one age group is discussed later.) There are at least four possible explanations of this excess.

(1) Schizophrenia has a hereditary basis, and the metabolic abnormality concerned is present from birth. As a result excess melanin is formed from the beginning, and the subjects show an undue proportion of the dark haired type. This implies that in schizophrenics with fair hair the disease must have some cause other than adrenochrome intoxication.

(2) Schizophrenia has a hereditary basis, the gene responsible being on the same chromosome as that for dark hair. This does not attribute the dark hair to the metabolic abnormality responsible for schizophrenia, but only implies linkage between the two genes and therefore provides an explanation of the fact that all schizophrenics do not have this hair colour.

(3) It might be supposed that as the excess of dark hair is statistically significant there should be a significant deficiency of blonds. (It must be remembered that the definition of blond is blue eyes and fair hair.) This is not necessarily the case. Eye colour in man is generally regarded as being fixed within a few months of birth, but it has been shown by Riddell (1942) that there is a change with advancing age, the pattern of the iris becoming more complex with a general appearance of deepening of colour. This change, however, requires special examination to demonstrate it, and it has not been possible to show it within the age limits of the present series. On the other hand the darkening of hair with age is marked (Steggerda, 1941), and is well shown in the control series. Therefore the excess of dark hair in schizophrenics does not necessarily mean that the subjects have been dark from birth. Their eye colours do not now differ from those of the control series, possibly their hair colours did not do so at birth, and the excess of dark hair now found would be due, not to a hereditary factor but to increased melanin formation from the excess of adrenochrome. It is to be noted that the symptoms of schizophrenia appeared one to three years after the recording of the eye and hair colours. This implies that (*a*) the excess of adrenochrome has not been present from birth, but (*b*) it was present for some time (years) before the development of obvious schizophrenic symptoms. This possibility again provides no explanation of schizophrenia in blonds, other than a different cause.

(4) The fourth alternative arises from a consideration of evidence from previous work on schizophrenia and other subjects.

(*a*) Bellak (1947) has summarized the evidence from investigations of liver function in schizophrenics. Although there is still disagreement on hippuric acid excretion, there is a body of facts providing firm evidence of impairment of liver function in this disease. Of particular interest here is the description by Hoffer, Osmond and Smythies (1954) of an unpleasant experience of a volunteer for experimental adrenochrome psychosis, which was attributed to the results of a previous attack of infective hepatitis, and has caused these authors to issue a warning against such experiments in persons with a history of liver disease.

(*b*) There is no firm evidence of an over-production of adrenaline in schizophrenics, and in fact what evidence there is suggests that there may well be a deficiency. Conclusions may also be drawn from the negative evidence provided by cases of tumour of the adrenal medulla. The twenty-three papers on this tumour quoted by Ackerman and Regato (1947) have been searched, and in no case has there been found any description of symptoms which could be regarded as schizoid in character. It follows that over-production of adrenaline *per se* is not an adequate explanation of the hypothesis that adrenochrome is the cause of schizophrenia, as in these cases of medullary tumour there is a gross excess of adrenaline but no evidence or even suggestion of any abnormality in the subsequent metabolism of this substance. It then becomes necessary to assume an accumulation of adrenochrome in the schizophrenic subject because of blocking of one or more of the paths of adrenaline detoxification. These paths are (Bacq, 1949):

1. Excretion unchanged in the urine.
2. Storage within cells.
3. Deamination and subsequent oxidation of the side chain.
4. Esterification of the phenolic hydroxyl groups.
5. Oxidation through adrenochrome to melanin.

There are no grounds for assuming that (1) and (2) are affected, and the activity of (5) is the basic hypothesis under investigation. There remain (3) and (4), both of which probably take place in the liver. It follows that a damaged liver could result in diversion of unusual amounts of adrenaline to path (5), with a necessarily higher than normal concentration of adrenochrome in the body.

(*c*) It has been shown (Lea, 1953) that there is a highly significant excess of the dark type of individual in cases of trophopathic hepatitis. (*Trophopathic* hepatitis is defined as necrosis of the liver due to deprivation of some substance essential to the life of the cells, in contrast to *toxipathic* hepatitis which is necrosis due to the direct action of some toxin, whether chemical or bacterial (Himsworth, 1947). It was suggested that this association was due to a hereditary metabolic abnormality linked with colour rather than to two different effects of one gene. There was no evidence of such an association in cases of toxipathic hepatitis.

The fourth explanation may now be formed as follows: it is suggested that in persons with a hereditary liver defect, or in those who have suffered damage to the liver as a result of toxipathic hepatitis, the metabolic path leading through adrenochrome to melanin would carry more adrenaline than is usual. As a result the concentration of adrenochrome in the body would rise, with the production of the symptoms constituting schizophrenia. The preponderance of the dark type of individual in this disease would then be due to the known association with trophopathic hepatitis; the presence of the blond type would be attributed to liver damage resulting from toxipathic hepatitis in this pigmentary type. In other words, schizophrenia would be yet another example of a state that may be produced by either hereditary or environmental factors, the end results of the two causes being indistinguishable.

It was noted that many of the cases of schizophrenia used in this investigation had infective hepatitis within two years of the onset of mental symptoms, and it was at first thought that this might provide confirmation or otherwise of the above suggestion. However, it soon became clear that the population under investigation had been exposed to an abnormal risk of contracting infective hepatitis, due to the fact that so many of them had served in areas in which epidemics of the disease had occurred, so that any results obtained would necessarily be biassed and valueless.

*The limitation of the excess of dark haired subjects to the age group 15–19 years.*

Two obvious explanations present themselves:

(1) That included in the syndrome known as schizophrenia are at least two distinct conditions, (*a*) one due to intoxication by adrenochrome or some related substance with an average age of onset of less than 20 years, and (*b*) the other due to some other cause or causes with an average age of onset of at least 30 years.

(2) That schizophrenia is a single disease, due to adrenochrome or similar intoxication, but with two modes of origin, (*a*) hereditary factors with an average age of onset of less than 20 years, and (*b*) environmental factors, e.g. liver disease, which may operate to produce schizophrenia at any age.

Unfortunately, schizophrenia is so extremely varied in its manifestations that it might very well consist of a number of different diseases. The position is so confused that it must be stated, on the one hand, there is no proof whatever that schizophrenia is a single disease, nor, on the other, is there any proof that it does contain a number of different entities. Certain pointers appeared in the course of the present investigation, one of them being the presence of two maxima in the age incidence at about 20 and 30 years, another that whereas the group with the earlier onset tended to undergo steady deterioration with eventual death in an institution from intercurrent infection, the group with later onset suffered little intellectual impairment, did not remain in institutions, and not infrequently died by suicide. However, investigation of both these trends failed. On the age distribution, it is clear that service personnel are strictly limited to certain age groups, and that the average of 20 years is too high because of the absence of age groups below 17, and that 30 is too low because of the absence or rarity of the groups over 50. It must also be remembered that the frequencies in the age groups which are represented in the services are not distributed as they are in the general population, and it is quite possible that if they were truly representative the two observed maxima would merge into one. On the question of the course and end of the disease it became evident that the younger age groups were still far too young for any firm statements to be made about their progress. Whether these apparent trends are anything more than the results of selection can only be determined by a long-term investigation of unselected material from the general population.

*The negative association with allergy.* There is little to add on this point except to emphasize that the deduction made from the adrenochrome hypothesis was fully confirmed by the evidence. However, consideration of Lucy's work on histamine tolerance, on which this deduction was based, showed that a further approach to the question of the homogeneity or otherwise of schizophrenia could be made. Lucy gave data from 50 cases of schizophrenia, dealing with them from the point of view of whether the histamine tolerance became less with the duration of the disease, and found that there was no evidence of such a lessening. From this he concluded that even after 25 or more years the disease was still the same. But these data can also be regarded from the point of view of whether or not the abnormal histamine tolerance is associated with the age at onset of the disease. Clearly if this increased tolerance were associated with only the younger age groups this would provide evidence for the view that schizophrenia contains more than one disease. The data were rearranged for this purpose and the correlation between the age at onset and the maximum amount of histamine tolerated was examined. The correlation coefficient between these two factors was found to be $-0 \cdot 03$, a value which does not even approach a significant level, The evidence from Lucy's work therefore lends no support to the view that schizophrenia is a syndrome containing more than one disease.

## CONCLUSIONS

Using the view that schizophrenia is due to intoxication by adrenochrome as a working hypothesis certain conclusions can be drawn from this investigation.

The two deductions, that a population of schizophrenics should show an increased incidence of dark pigmentation and a decreased incidence of the allergies, have been confirmed. These results support the hypothesis of adrenochrome intoxication but the limitation of the excess of dark hair to the age group 15–19 years requires further explanation. Of the explanations suggested it is considered that the evidence is most consistent with the hypothesis that the metabolic fault is due to hepatic insufficiency, and that this may be due to either hereditary or environmental factors. This explains the preponderance of dark types in the age group 15–19 years (hereditary), the presence of other pigmentary types at all ages (environmental), the evidence of liver damage in schizophrenics, the persistence of abnormal histamine tolerance throughout the course of the disease and the absence of a correlation between age at onset and degree of histamine tolerance. It is also consistent with the view, supported by re-examination of Lucy's data, that schizophrenia is a single disease. No suggestion is made that this hypothesis of liver dysfunction as the cause of the excess of adrenochrome has been established, nor does it seem possible to investigate it further with the material on which this paper is based. The hypothesis is put forward as one which offers an explanation of the observed data, but at the same time only too clearly emphasizes that many, possibly most, of the facts of schizophrenia are still unknown. It will be noted that the grounds on which the presence of an excess of dark types was originally deduced have now been discarded in favour of the hypothesis of liver dysfunction.

## SUMMARY

(1) Accepting the views of Hoffer, Osmond and Smythies, that adrenochrome or some related substance is the cause of schizophrenia, as a working hypothesis, the deductions were made that a population of schizophrenics should contain an excess of deeply pigmented types and a deficiency of persons with allergy.

(2) 1,008 cases of schizophrenia and two control series, one of 5,127 cases of all types of injury, the other of 500 cases of head injury, have been investigated. It was found that there was a highly significant excess of dark hair in the schizophrenics, limited to the age group 15–19 years, and that there was a highly significant deficiency of allergic conditions.

(3) Explanations of these findings have been discussed, and the suggestion made that the evidence is most consistent with the view that the excess of adrenochrome is due to hepatic dysfunction, both hereditary and acquired.

(4) Re-examination of Lucy's data on histamine tolerance in schizophrenics supports the view that schizophrenia is a single disease.

(5) Other deductions have been made from the working hypothesis, but they cannot be investigated on the material available. Their investigation would help to establish, or disprove, the adrenochrome hypothesis.

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# AN INVESTIGATION OF HUNTINGTON'S CHOREA IN VICTORIA

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In making an investigation of Huntington's Chorea in the State of Victoria, we have, so far, been able to collect 150 indisputable cases of this disease, and others. This figure includes 83 deceased, and 57 living. Out of a total of 74, who were certified to mental hospitals, 26 are still either in hospital or on trial leave. This represents ·34 per cent. of the total present mental hospital population. As regards sex distribution, our figures indicate that there were 68 females as compared with 72 males.

As far as can be ascertained, the first recorded case of Huntington's Chorea occurring in Victoria was at the Yarra Bend Mental Hospital in 1878. Although diagnosed then as Choreic Dementia, the clinical description of the patient and the subsequent family history leave no doubt that the case was one of Huntington's Chorea. Victoria, which was first settled in 1834, must be regarded as a new country and one which has been subject to the impact of a continual migration from other parts of the world, particularly Great Britain. There are three recognized peaks in this migratory flow; during the Gold Rush of the 1850–60s, and after each of the two World Wars. The changing population has created many difficulties in our investigations, and consequently in quite a number of instances it has been impossible to trace either the predecessors, or all of the descendants of known cases of Huntington's Chorea. However, it seems clear that there have been multiple sources responsible for the introduction of this family disease into Victoria, from older countries as well as from other Australian States. Restlessness and a wandering disposition, so frequently found in numbers of Huntington's Chorea families, have no doubt contributed appreciably to the relatively large number of the descendants of affected

TABLE I

| Country of Origin | Number of Families | Number of Cases in Victoria |
|---|---|---|
| England: | | |
| Cumberland | 1 | 18 |
| Northumberland | 1 | 8 |
| Cornwall | 3 | 14 |
| London | 2 | 9 |
| Scotland | 3 | 8 |
| Ireland | 2 | 18 |
| Germany | 1 | 3 |
| Tasmania (*ex* England) | 1 | 9 |
| Total | 14 | 87 |

families migrating to any country, and, on arrival, moving about from place to place. In those instances where it could be definitely established, the country of origin of various Victorian families, and the number of cases found among the descendants of these families, is given in Table I.

TABLE II

*Isolated Huntington's Chorea Cases whose Families are Non-Resident in Victoria*

| Country of Origin | No. of Cases |
|---|---|
| Italy | 1 |
| Canada | 1 |
| New Zealand | 1 |
| Australia: | |
| New South Wales | 5 |
| South Australia | 3 |
| West Australia | 3 |
| Queensland | 1 |
| Tasmania | 7* |
| Total | 22 |

There were 39 cases of Huntington's Chorea in which the country of origin was unknown, and of these there were five cases who were adopted or illegitimate.

## AGE AT ONSET OF FIRST SYMPTOMS

In the 73 cases where the age of onset was determined with a degree of accuracy, the average age was 38·3. The following table shows the age of distribution.

TABLE III

| Age Range—Years | No. |
|---|---|
| 0– 9 | 0 |
| 10–19 | 3 |
| 20–29 | 13 |
| 30–39 | 28 |
| 40–49 | 21 |
| 50–59 | 6 |
| 60–69 | 2 |
| Total | 73 |

The average age of onset was given by Davenport (1916) as 37·8; Julia Bell (1934) 35·5; Minski and Guttman (1938) 42·4.

## EARLY SYMPTOMS

In the 65 cases in which detailed study was possible, 33 presented neurological symptoms as the mode of onset; in 16 cases mental preceded neurological symptoms, and in the remaining 16 cases both neurological and mental symptoms appeared within such a short interval of each other that it was impossible to state accurately from the history available which did appear first. The most commonly found early involuntary movements in order of frequency were:

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* Six of the seven isolated cases from Tasmania are descended from one family which has 105 known cases of Huntington's Chorea. The original member of this family migrated from Somerset to Tasmania with her family of twelve in 1853 (Brothers (1950)).

- Fidgetiness
- Motor restlessness
- Swaying and staggering gait
- Jerkiness of the head
- Shrugging of the shoulders
- Clumsiness of hand movements
- Twitching of facial muscles

In several instances, early involuntary movements appear to be confined to a relatively small group of muscles for several years before the occurrence of gradual involvement of other muscular groups. In the majority of cases, however, once any involuntary movement had become manifest, gradual extension of choreiform movement to other skeletal musculature was the rule, resulting eventually in the almost incessant severe generalized choreiform movements characteristic of this disorder.

The most frequently found psychological disturbances were irritability and quick temperedness. This was the case in nearly 70 per cent. of cases where the appearance of the mental symptoms preceded the chorea. Other early abnormalities which were responsible for bringing the patient under notice were as follows:

- Moodiness or depression
- Abnormal excitability
- Emotional apathy
- Paranoid trends
- Outbursts of violence
- Irresponsibility
- Defective concentration and memory
- Loss of moral control resulting in erotic behaviour, delinquency, or alcoholism
- Aimless wandering and vagrancy, and, in one particular instance, compulsive behaviour

## Mental States Associated with Huntington's Chorea

Although the mental picture of Huntington's Chorea is that of progressive organic dementia, it is often preceded by emotional disturbances and changes of personality, amounting, at times, to progressive psychotic states requiring certification.

### *Depression*

In our series there were seven cases whose admission to hospital was due to severe depressive states. Four showed depression prior to the onset of chorea, and three developed, subsequent to chorea. Suicide had been attempted in one of the first group and two of the second group. Two cases showed remission of the depression following electropexy. Of the four cases where mental symptoms preceded the physical, three developed chorea one year later, and the other, eight years later.

### *Mania*

Three cases were admitted to hospital on account of acute maniacal outbursts. One had had several attacks of mania during the twenty years preceding the onset of chorea. In each of the other two cases, chorea preceded the initial attack of mania. In all three, the attacks were definitely episodic and occasionally alternated with periods of mild depression.

### *Paranoid Reaction*

Of the seven cases with marked paranoidal features, five developed psychotic symptoms prior to chorea, and two subsequently. In the former the duration between onset of mental and physical symptoms varied between one and eight years. The progress of the initial dementia appeared to be somewhat slower in these cases than in the average cases of Huntington's Chorea. In no instance was there any amelioration of symptoms at any time.

### *Schizoid Reaction*

Four cases showed very typical schizophrenic-like psychosis with the usual symptoms of withdrawal, emotional displacement and auditory hallucinations. Three occurred prior to the appearance of chorea. Of these, one developed early signs of chorea within one year, and two showed evidence of chorea three years after the onset of mental symptoms. In the fourth case, as both neurological and psychotic symptoms were present on admission and the early history somewhat obscure, it was not possible to venture any opinion as to which appeared first.

### *Epilepsy*

Only two cases were admitted on account of mental symptoms associated with epilepsy, and both had been subject to seizures since late adolescence several years prior to the onset of chorea.

### *Mental Confusion*

In the cases of two brothers (Family F) the mental picture on admission was that of mental confusion, with marked clouding of consciousness. In these two cases choreiform movements had not been apparent prior to the onset of confusion, but were certainly present in a mild form shortly after admission. Both cases progressed to increasing dementia without any amelioration of symptoms.

### *Mental Deficiency*

Apart from three instances of Huntington's Chorea occurring in cases of low grade feeble-minded members of known Huntington's Chorea families, two other familes have been discovered in which chorea was associated with mental deficiency. In each instance, there was no evidence of Huntington's Chorea having occurred in previous generations. Consequently, until further investigations can be carried out, it is premature at the moment to regard them as cases of Huntington's Chorea, although when seen as adults they are apparently indistinguishable from typical cases of this disease. In one family (Plate 1), the parents, who were of Cornish stock, were first cousins. There

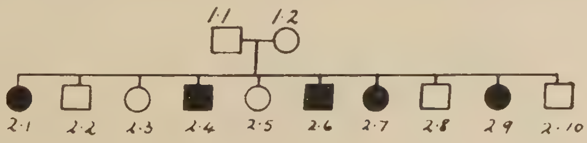


PLATE 1

were ten siblings in the generation investigated. Five of these were affected with chorea, and the other five were reported as being mentally and physically normal. Each of the five affected members was a mental defective of imbecile level and had had choreiform movements since infancy. The first affected member of this family at the age of eighteen was described by the Commonwealth Medical Referee as having been mentally defective since birth, and as suffering from chronic chorea. It was particularly stressed at the time that there was marked unsteadiness of the head and limbs. Thirty years later, at the age of forty-eight, this patient was admitted to Mont Park Mental Hospital physically helpless as a result of gross generalized choreiform movements. The fourth member of this family, an imbecile of low grade, is reported as having had muscular twitchings since infancy. At the age of twenty-five he was admitted to Sunbury Mental Hospital, grossly choreic. There was marked irritability and inability to sit still, facial twitchings, marked dysarthria, and choreiform movements. The sixth member of the family was admitted to Sunbury Mental Hospital at the age of twenty-four, when he was diagnosed as a high grade imbecile with chorea which had been present since the age of three. There was unsteadiness in gait and constant choreiform movements involving the whole voluntary musculature. Death occurred seven years later at the age of thirty. Information regarding post-mortem findings in this case is not available. Unfortunately, in the past, there does not appear to have been any systematic attempt to study in detail any of the post-mortem specimens of brains from choreic subjects. The seventh member has been reported by a social worker as being a mental defective with chorea. This patient is still living at home and no further details are available. The ninth member was admitted to Sunbury Mental Hospital at the age of sixteen, when he was described as an imbecilic youth with continuous choreiform movements of muscles, head, face, limbs and trunk. Information given by relatives suggested that the choreiform movements had been noticeable since at least the age of three.

In the second family (Plate 2), the parents, both of whom originally came from Devon, England, were second cousins. Neither the father, who died at the age of eighty-two, nor the mother, who is still alive, aged eighty, apparently showed any signs of chorea. There were eight siblings in the family. The first died as a result of meningitis in infancy. Cases 2.2 and 2.3, who were identical twins, were mental defectives (feeble minded). The history relates that they had had an indistinct and slurred speech from childhood. In their early adult lives they were able to perform domestic duties of a routine nature, but at approximately the age of forty they began to show mental deterioration, and being unable to care for themselves were admitted to the Ballarat Mental Hospital. It was about this time that choreiform movements were first definitely noticed. At the time of death, several years later, both were completely bedridden on account of gross chorea. Case 2.4 is reported as being normal. Case 2.5, who

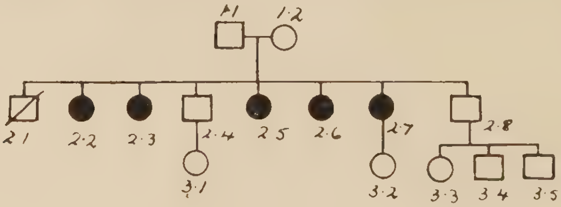


PLATE 2

was an epileptic mental defective, died in the Kew Mental Hospital at the age of sixteen. Case 2.6, also an epileptic defective, died in the same hospital at the age of eighteen. Case 2.7 was a congenital mental defective (feeble minded) who was admitted to Royal Park at the age of forty-three, at which time she was showing evidence of being mildly choreic. Case 2.8 is reported as being of good intelligence and shows no signs of chorea.

## Diagnosis and Prediction

In the absence of details of family history, mistaken diagnoses are most commonly found in early cases where the mental symptoms have appeared prior to the onset of choreiform movements, or, where the latter are so mild as to have been overlooked at the time of examination. A number of such cases in our series have been originally diagnosed as paranoid psychoses, schizophrenia, psychopathic states, neuroses, depressive states, dementia, and mental deficiency. Even in more advanced cases where chorea is manifest but family history obscure, occasional misdiagnoses are made, the most common instances being when they have been mistaken for post-encephalitis, general paralysis of the insane, disseminated sclerosis, senile and Sydenham's chorea.

On the other hand, in a few instances, certain cases originally diagnosed as Huntington's Chorea have subsequently proved to be cases of either hysteria, adult mental deficiency with chorea, or reactive depression. The depressive states may occur as symptoms of Huntington's Chorea, but, at the same time, it is realized that there is a marked tendency for reactive fears of family ill health and disease to occur in unaffected members of such families.

In well established cases where the choreiform movements are marked, and the family history is known, the diagnosis presents no difficulty. However, there still remains the problem of ascertaining which of the as yet unaffected members of a "Huntington's family" are likely to succumb to the disease. Since Huntington's Chorea has been shown to be a Mendelian dominant, it is clear that the probability is one in two that any descendant will be affected. It is obvious that years of apprehension and anxiety would be obviated for non-affected members if means could be found of predicting which individuals were not likely to become victims.

The use of EEG and psychological tests suggested themselves as possible methods of obtaining criteria for prediction.

Regarding the EEG, we are most grateful for a personal communication from Dr. J. Daniel Palm, of the Dight Institute for Human Genetics, University of Minnesota, in which he states:

> "The information we have of test results of affected persons is indeed scanty and in need of further verification. An antithesis apparently exists in the EEG tests. In the very early stages of the disorder the persons show an abnormal EEG of the low voltage fast type which is also present in half of the adult offspring of affected persons. We believe that destruction of the connection of the caudate to the thalamus by the ravages of the disease may interrupt the feed back system to area IV and thus give a normal EEG. This hypothesis is certainly open to criticism, but is all that we have now.
>
> "We have administered various psychological tests to the offspring of choreics but only one test seems to show promise. The Rorschach Ink Blot tests show a significant number of abnormal personality traits present in the group tested but are not correlated with the EEG."

In this department it was thought that, in addition to assisting diagnosis and indicating rate of deterioration, the comparison between the psychological tests of affected and non-affected members of Huntington's descendants might yield some clue as to which unaffected members were likely to be affected.

With early affected cases it was possible to apply the Wechsler (1939), Rorschach (1937), Goldstein Colour Form (1941), Cattell 16 P.F. (1946), Cornell Index (1945), and standardized tests of educational attainment and writing. With advanced cases of the disease it was sometimes only possible to complete one or two of the sub-tests of the Wechsler, generally repeating digits, arithmetic, and information, and to obtain a word recognition index (Burt's Reading Scale) (1922).

An examination of the Wechsler results from thirteen of the earliest cases of the disease indicated that at first the Huntington's Chorea patient retains his ability to recount general information, and he understands and makes use of his everyday vocabulary. On the other hand his ability to manipulate numbers and his immediate rote memory show considerable deterioration, with the earliest onset of physical or mental symptoms. On the whole the patient does very much worse on performance tests. The greatest reduction is shown in (1) the ability to analyse and synthetize perceptions (Block Design test), and (2) learning association flexibility and motor co-ordination (Digit Symbol test).

Use of the Wechsler formula indicated with this group that deterioration ranged from 14 per cent. to 80 per cent., mean 43 per cent. (S.D. 19 per cent.). There was also a small positive correlation between the amount of deterioration and the duration of the disease.

In two cases of the disease it was possible to retest the patients with a two years' interval. The results suggest that there is an irregular decline of one to two points of weighted score per year in the "Don't Hold" Wechsler tests at the early stages of the disease.

The Rorschach test, although applied to only a few of the earliest affected cases, invariably gave a record characteristic of organic lesion, namely poor output, percentage of "F" higher than normal, absence of "FK", slow reaction times, little or no "M", colour naming, impotence, perplexity, and use of automatic phrasing.

The Inventories, Cattell 16 P.F. and Cornell N.2, revealed in detail personality dysfunction of the affected compared with the unaffected, and supported the general picture given by the psychiatric examination.

The results of educational tests indicated a definite falling off in the affected in the ability to make arithmetical calculation. In the same group there was also a decline in word recognition, which was equal on the average to the difference between an Eighth Grade, compared with a Sixth Grade educational level.

In all cases where samples of handwriting were taken of the affected group it was obvious that the choreiform movements interfered with the writing to a greater or lesser degree, producing in many cases a characteristic "saw tooth" effect.

The testing of a small number of children from Huntington's families yielded insufficient data on which to base any positive hypothesis. However, the test results of an unaffected descendant, aged 37, were remarkably similar to those of undoubted cases, for example, three of the Wechsler tests associated with deterioration were significantly lower than expected. This person showed physical symptoms of the disease two years later.

## PROGNOSIS

Once established, the chorea progressively becomes worse. There are no remissions, although in certain families its progress is much slower than in others. In the terminal stages there is usually gross emaciation and weakness, and unless some inter-current illness intervenes they become chronically bedridden and eventually die as a result of exhaustion. Although in the large majority progressive organic dementia is usual, nine cases in our series showed no apparent personality change throughout the course of their illness. One (H. 2.1) who developed chorea at the age of sixty is still at the age of seventy-five very well preserved mentally, in marked contrast to his son who at the age of forty-four, five years after the onset of illness, is already showing marked mental deterioration. Six cases showed remission of the acute early mental symptoms necessitating their original admission to hospital, but in each case there was probably some slight residual deterioration—one was able to remain at home for nearly twenty years, and another twelve years, before being readmitted in an advanced state of dementia.

Based on thirty-six cases in which the ages of onset and of death were both ascertained, the average duration of the disease was thirteen years. The shortest duration was one instance in which death was recorded after only two years of symptoms; the longest fifty years. The duration of the disease did not appear to be influenced by the age of onset. The average age at death which was established in fifty-seven cases was 51·3 years. Table IV shows the age distribution of death.

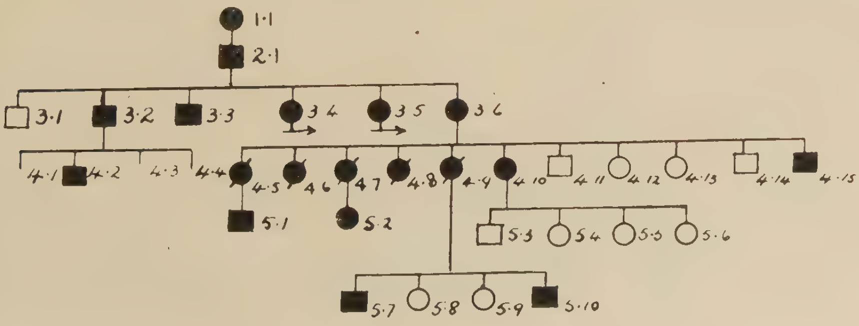
TABLE IV

| Age Range—Years | No. |
|---|---|
| 0–10 .. .. .. .. | — |
| 11–20 .. .. .. .. | — |
| 21–30 .. .. .. .. | 1 |
| 31–40 .. .. .. .. | 6 |
| 41–50 .. .. .. .. | 18 |
| 51–60 .. .. .. .. | 20 |
| 61–70 .. .. .. .. | 7 |
| 71–80 .. .. .. .. | 5 |
| Total .. .. .. | 57 |

## EXAMPLES OF FAMILY HISTORIES

### *Family "A"*

The first recorded case of Huntington's Chorea occurring in the State of Victoria was a male patient (Plate 1) (Case 2.1) who, at the age of 41, was admitted in the year 1878 and died 12 years later at the Ararat Mental Hospital. He was stated to have migrated from the County of Cumberland, England, where his mother was supposed to have died from a similar illness some years previously. As far as is known, there were no siblings. In the following generation, there were six siblings and interestingly enough all but one were apparently afflicted with Huntington's Chorea. There is no record, however, of any of them having been admitted to a mental hospital. There are no known descendants of Cases 3.1 and 3.3. As regards Cases 3.4 and 3.5 there were descendants, but no information concerning them has been obtained. Case 3.2 had four children, two of whom were diagnosed at the Sunbury Mental Hospital as cases of Huntington's Chorea, one of whom (Case 4.2) was originally an epileptic mental

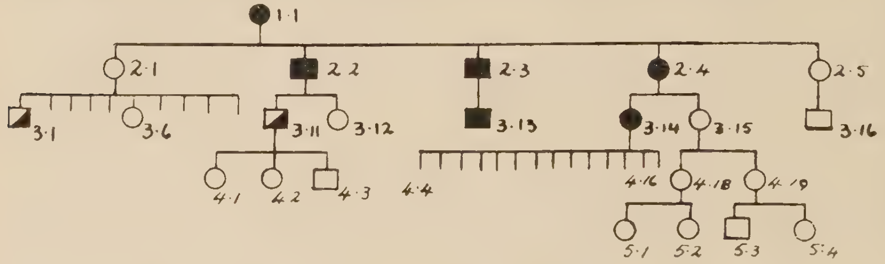


defective. By the time he had reached the age of 17, he was grossly choreic. Case 3.6 had eleven children, the six eldest (4.5 to 4.10) and the youngest (4.15) all of whom eventually developed Huntington's Chorea. The age of onset of these seven cases was uniformly about thirty-five and the age of death approximately forty-five, the deaths being manifest by chorea followed by simple dementia. Cases 4.5, 4.6 and 4.7 died in benevolent homes. Cases 4.8, 4.9 died in mental hospitals, while Case 4.10 is still alive in a mental hospital.

In the present generation, Cases 5.1, 5.2, 5.7, 5.10, have already been admitted to mental hospitals with the diagnoses of Huntington's Chorea. In three of these cases the early mental symptoms were somewhat schizoid in nature, and in each case there was marked violent behaviour immediately prior to admission to hospital. Cases 5.8, and 5.9, as yet show no apparent mental change or choreiform movements. The age of onset in this generation was 31, 23, 21 and 18 respectively. Cases 5.3, 5.4, 5.5 and 5.6 whose present ages range from seven to twenty-five years, are as yet still unaffected.

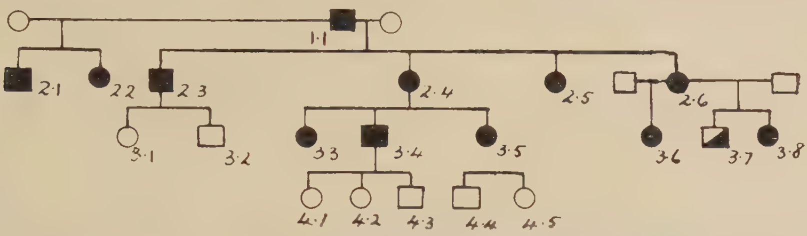
*Family "B"*

Case 1.1 arrived in Victoria from Northumberland some time during the middle of the second half of the nineteenth century. She was the only member of her family to migrate to Australia. Although showing definite evidence of chorea before she died, there were apparently no gross mental changes. Her eldest daughter (Case 2.1) together with her family of ten children, lived in New South Wales. She died at the age of seventy, somewhat mentally enfeebled, but apparently not choreic. This is not conclusive as no really reliable information could be obtained. Her eldest son (Case 3.1) died in a New South Wales mental hospital before the age of forty. No data is available about the other siblings, except in Case 3.6, who is known to be free from chorea at the present time. Case 2.2 died of Huntington's Chorea in a benevolent home. There were two children, the elder of whom was showing early signs of chorea four years ago. Case 2.3 died as the result of Huntington's Chorea in a benevolent home. His only son (Case 3.13) was admitted to Mont Park Mental Hospital at the age of forty-two in an advanced stage of Huntington's Chorea and died five years later. Case 2.4, who died at the age of fifty from Huntington's Chorea, showed no gross mental abnormality. Her eldest daughter (Case 3.14) at the age of thirty-nine developed marked irritability and became subject to outbursts of uncontrollable temper. Shortly afterwards, she developed choreiform movements of arm, head and face. A year later she was admitted to Mont Park Mental Hospital, where she rapidly deteriorated mentally and physically and died three years later at the age of forty-three. There were fourteen children, whose present whereabouts are unknown. Case 3.15, whose present age is fifty-two, is very tense and over-anxious but appears to be free from any suggestion of choreiform movements, although two years ago was regarded as an early case of Huntington's Chorea. Her two children, 4.18 and 4.19, are reported to be neurotic. The youngest sibling of the second generation (Case 2.5) died as a result of cerebral haemorrhage.



*Family "C"*

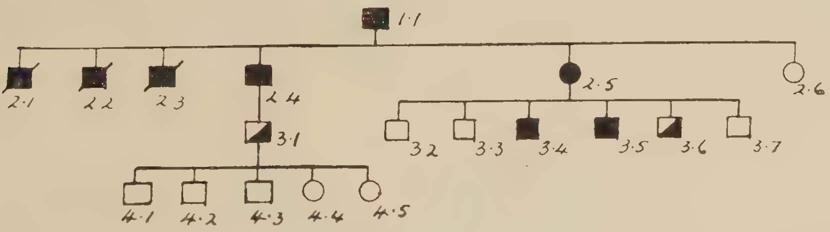
Little is known concerning the original affected member of this family beyond the fact that he was described as being nervy and probably of Irish extraction. It is presumed that he had chorea, and this is supported by the fact that all of his six immediate descendants (two by his first marriage and four by his second) have proved to be cases of Huntington's Chorea. In the first family (Case 2.1) an invalid pensioner, has marked choreiform movements. Case 2.2 is alleged to be very nervy and mildly choreic. Case 2.3 (second family) was admitted to the Kew Mental Hospital at the age of fifty-one, when he was markedly mentally enfeebled and practically helpless on account of advanced chorea. He died several months later. Case 2.4, according to her husband, began to exhibit mental changes at the age of twenty-eight, when she was hallucinated and developed delusions of poisoning. Later she began to show fidgety movements. On account of suicidal threats and violence towards her husband she was admitted to a mental hospital four years later. She remained in hospital for seventeen years until she died at the age of forty-nine. Case 2.4 was admitted to Kew Mental Hospital in her late twenties as a case of Huntington's Chorea. Case 2.6 is reported as having had a nervous breakdown at the age of eighteen, and apparently recovered. She attempted suicide twelve years later, after which she began to show signs of irritability, mental deterioration, and signs of chorea in the nature of facial twitchings, dysarthria, and unsteadiness of gait. On admission to hospital at the age of thirty-five she showed mild right hemiparesis. Death occurred at the age of forty-five. In the succeeding generation, nothing is known concerning the medical history of the children, 3.1 and 3.2. Case 2.4 had three children, still alive, but all affected by Huntington's Chorea (3.3 to 3.5). The eldest, 3.3, was admitted to Sunbury Mental Hospital at the age of thirty-nine, but the onset of the condition had been noticed approximately three years previously after an attempted suicide, shortly after which she began to develop choreo-athetoid movements. She became extremely irritable, abusive, destructive, and had attacks of uncontrollable temper. At the time of admission she had developed visceral delusions. She is now showing evidence of progressive mental enfeeblement. The second child (Case 3.4), is at present attending a general hospital on account of staggering gait and severe headaches since the age of thirty-six. The third child (Case 3.5) is described by her parents as being very irritable, and recently having developed a peculiar staggering gait at the age of thirty-six. Case 3.6 is the only issue of the first marriage of Case 2.6. She was admitted to the Ararat Mental Hospital at the age of twenty-four presenting schizoid features and early signs of chorea. Nine years later, just prior to death, she was extremely demented and physically helpless on account of advanced chorea. Case 3.7 (issue of second marriage of Case 2.6) is reported as being an invalid pensioner, who "sways about all over the place". Case 3.8 was admitted to the Ballarat Mental Hospital at the age of twenty-six when the clinic records reveal her as being unco-operative, refractory, regressive, delusional and hallucinated. She was originally regarded as a case of schizophrenia, but several months later it was noted that she had developed mild twitchings of the shoulders and fidgetiness of the hands. One year later the florid mental symptoms had somewhat abated, but there was some mental enfeeblement. The choreiform movements, on the other hand, had become much more pronounced.



It is interesting to note that, apart from the members of the last generation, whose ages are still below twenty, and Cases 3.1 and 3.2 about whom no information is available, Huntington's Chorea has been diagnosed in every member of this family.

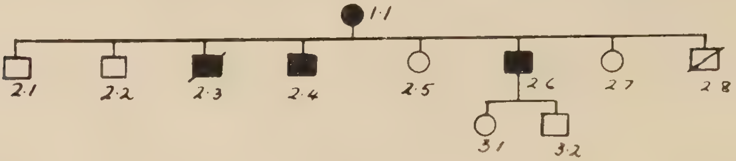
*Family "D"*

The earliest member of this family known to us to have suffered from Huntington's Chorea was an English migrant whose family formerly resided in the County of Cornwall. Clinically, little is known of this particular case beyond the fact that he died in early middle age from Huntington's Chorea. Of his six children, all but the youngest, who is still alive, developed signs of chorea at about the age of forty. A son, 3.1, is said to have been nervous and committed suicide. Case 2.5 lived for over twenty years after the onset of the symptoms. Apparently none of them showed any gross abnormality. In the next generation, information is available in the case of the descendants of Case 2.5. Two of her six sons (Cases 3.4 and 3.5) are at present suffering from advanced chorea, and another son (Case 3.6) is now showing early mild symptoms of this condition. Case 3.4 developed choreiform movements four years prior to his admission to Royal Park on account of repeated maniacal outbursts. On examination, there was marked dysarthria, twitchings of the face, and gross purposeless movement of the neck and arms. Mentally, he is euphoric, distractible, and exhibiting flight ideation, lack of attention, and memory defect. Whilst knowing all about the hereditary nature of his complaint and his own family history, he nevertheless appears to be quite lacking in any insight into the severity and seriousness of his own condition. Case 3.5, although markedly choreic, is still able to carry on his usual occupation as a wharf labourer.



*Family "E"*

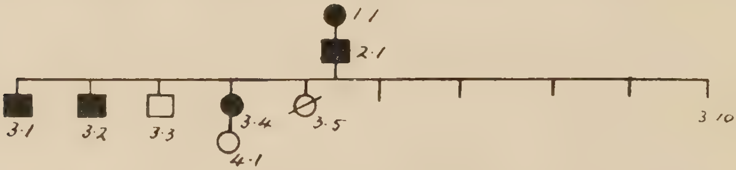
The Case 2.6 in family "E" was formerly a resident of New South Wales where his mother (Case 1.1) and two brothers (Case 2.3 and Case 2.4) were known to be definite cases of chorea.



He himself was admitted to the Kew Mental Hospital at the age of forty-one, grossly choreic and mentally enfeebled. The outstanding early mental symptoms described in this case were uncontrollable fits of temper and aimless wandering. Death occurred twelve years later at the age of fifty-three. He was the father of two children whose present whereabouts and clinical histories are unknown.

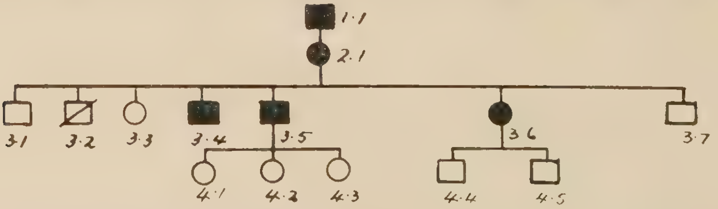
*Family "F"*

Case 1.1 died in an English Mental Hospital apparently from Huntington's Chorea. The son (Case 2.1), who migrated to Victoria, was admitted to the Sunbury Mental Hospital at the age of sixty-six and died three years later grossly demented and choreic. Information regarding duration of illness, early signs and symptoms, is not available. In the succeeding generation there were ten siblings. Of these, three were afflicted with Huntington's Chorea and one died from rheumatic fever at the age of eighteen. The others are reported as being in good health. Case 3.1 was admitted to Ararat Mental Hospital in an advanced stage of Huntington's Chorea when aged forty-seven, and he died at the age of fifty-four. Case 3.2 was admitted to the same hospital at forty-three and died four years later. Case 3.4 was admitted to Mont Park at forty-one, five years ago. All these cases were grossly demented on admission. The onset in each case was that of simple mental deterioration associated with mental confusion and early choreiform movements.



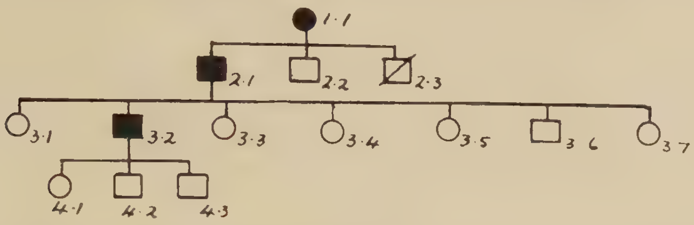
*Family "G"*

Apart from the fact that Case 1.1 died as a result of Huntington's Chorea, no further information is available regarding him or his antecedents. Case 2.1 died at the Royal Park Mental Hospital. The family consisted of seven siblings, of whom Case 3.1 is living in Canada, Case 3.2 was killed whilst a young man under the age of thirty, Case 3.3 and Case 3.7 are reported as being normal. Case 3.4 originally diagnosed as a case of multiple sclerosis, eventually died at the age of sixty-six from Huntington's Chorea. The fifth member, Case 3.5, was admitted to the Bundoora Repatriation Mental Hospital, at forty-three, eight years ago. The onset of his condition was characterized by marked irritability and paranoid features which preceded the appearance of clumsiness and other features of chorea. Of his three children, whose present ages range between four and seventeen years, the only point of interest is the psychopathic behaviour manifested by the eldest. Case 3.6 died at Mont Park at the age of forty-three, where she was originally diagnosed as suffering from schizophrenia. Her subsequent history revealed that she was a case of Huntington's Chorea. Her two children, the eldest of whom is now twenty-six, as yet have not manifested any demonstrable abnormality.



*Family "H"*

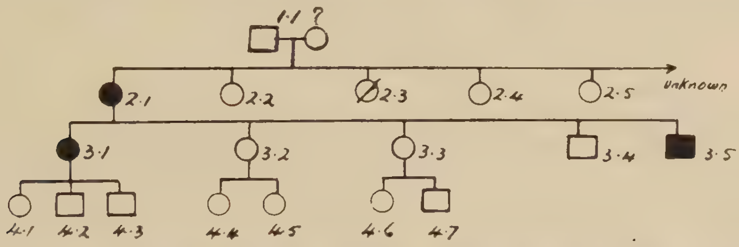
Family "H" originally came from Glasgow, Scotland. Case 1.1 spent a short period in a mental hospital in Scotland, but beyond the fact that she had chorea, no details of her condition are available. Of her three children, the eldest, Case 2.1, who migrated to Victoria with his seven children, developed signs of chorea at the age of sixty, when he was "paid off" from work on account of his physical inability to carry on the skilled operations of a glass cutter.



His present age is seventy-five, but there are no indications of any appreciable mental deterioration. The second member, Case 2.2, migrated to America, and the third, Case 2.3, died in adolescence. Of the seven children of Case 2.1, only one, Case 3.2, is known to have so far developed signs of Huntington's Chorea, which became manifest at the age of thirty-nine. Five years later he was admitted to Royal Park Receiving House grossly choreic. Mentally, he was described as being paranoidal and abnormally excited. Although no longer in hospital, he is now showing marked signs of mental enfeeblement. His three children, who are below the age of twenty, so far give no indication of the onset of Huntington's Chorea.

*Family "I"*

The parents of Case 1.1 came from Maitland, New South Wales. Unfortunately, there is no evidence to indicate that either of them suffered from Huntington's Chorea. It is known that they had a large family. We have been able to trace only three cases with Huntington's Chorea, and in each instance mental symptoms preceded chorea. Case 2.1 was described as being exceedingly jealous, violent tempered, and neglectful of her five children, and for some years prior to her admission to hospital, at the age of thirty-four, she spent most of the day in bed and completely neglected her household duties. She died at the age of forty-three, grossly choreic. Her eldest daughter, Case 3.1, under the age of twenty, was apparently a placid, even tempered, likeable, but somewhat gullible person. At about the age of twenty she became very erotic, neglectful of her appearance and household duties, threatened to commit suicide and injure the children. At the age of twenty-three, just prior to her admission to a mental hospital, she began to lose control of her legs. Dementia was rapid and profound, death taking place at the early age of twenty-nine. Her three children are below the age of ten years.

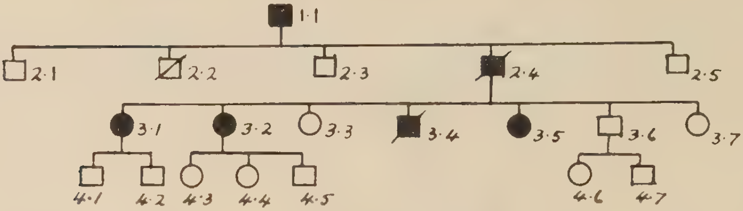


Case 3.2 is described as being a silly, giggling, "feather brained" girl, subject to violent outbursts of temper. There are as yet no signs of chorea.

Case 3.3 is known to be a prostitute. Case 3.4 is a stammerer who is very tense and over anxious. Case 3.5, the youngest member of this generation, is below average intelligence and sits for hours without speaking. He has definite twitchings of the face, and so it would appear that he is an early case of Huntington's Chorea. In those members of this family not yet diagnosed as suffering from this disease, the abnormal personalities could obviously be attributed to the deplorable environmental conditions—broken home—alcoholic father—years of poverty and neglect—as was the case in this particular family, but despite this they may still possibly be found to be also associated with Huntington's Chorea eventually.

*Family "J"*

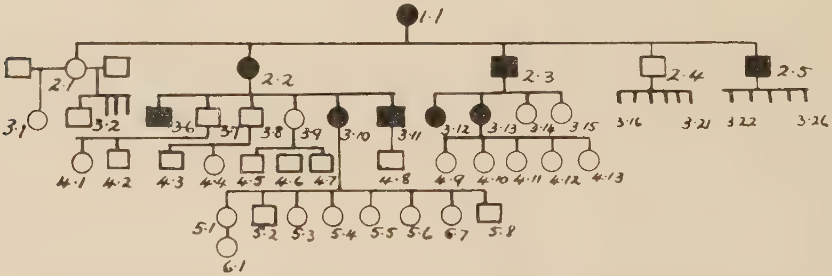
The original member of this family (Case 1.1) was born in County Clare, Ireland, and arrived in this country during the latter half of the last century. He is reported by his grandchildren as having suffered from "St. Vitus Dance". Of the first generation born in Australia,



Case 2.2 died in a mental hospital with the diagnosis of senile dementia. The only member of this generation known to have definitely suffered from Huntington's Chorea was Case 2.4. Of his seven children Cases 3.1, 3.2, 3.4, and 3.5 are all known to be suffering from Huntington's Chorea at the present time.

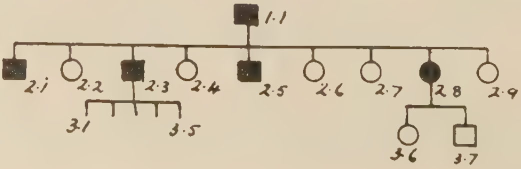
*Family "K"*

Case 1.1 arrived in Victoria from Tasmania, but it is reasonably supposed that she had originally migrated from England. At the age of fifty, she developed restlessness and choreiform movements. Death occurred twenty years later at the age of seventy. There is no record of any siblings being in this country. As a result of her first marriage, there were five children, three of whom developed Huntington's Chorea at approximately the age of forty. One of these (Case 2.2) spent a short period in a mental hospital. There was no issue of the second marriage. Of the six immediate descendants of Case 2.2, three developed chorea. Case 3.6 first showed typical choreiform movements at the age of forty-four and five years later began to show signs of mental enfeeblement and confusion. Cases 3.10 and 3.11 are as yet presenting early signs only of chorea without any apparent mental change. Of the descendants of Case 2.3, Case 3.12 was admitted to Royal Park Mental Hospital at the age of thirty-eight in an advanced state of dementia. The choreiform movements were gross and generalized, death occurring one year after admission. There was no issue of her marriage. Case 3.13 first showed signs of the disease at the age of thirty-two. Fourteen years later, at the time of examination, she was moderately demented and completely bed-ridden. There were five children of Case 2.5, but no information is available. The children of all affected members of the third generation are still below the age of twenty-two, and as yet there are no signs of the disease in any one of them.



*Family "L"*

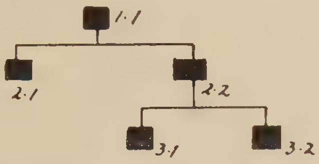
The original members of this family migrated from Germany to Victoria approximately ninety years ago. Nothing is know of their immediate descendants, except that a son (Case 1.1) and his family moved from Victoria to Tasmania early this century. He was admitted to the New Norfolk Mental Hospital at the age of fifty-five with a history of choreiform movements of the upper limbs and mental deterioration. Two sons (Cases 2.1 and 2.3) developed chorea and showed personality changes at about the age of forty, and both were subsequently admitted to the same hospital. Case 2.5 was admitted to Mont Park Mental Hospital at the age of 31, the provisional diagnosis being general paralysis of the insane. It was later revealed that his Wasserman reaction was negative and that he had been subject to epilepsy for a number of years. On examination, there was a stumbling gait, slurred speech and at



times a marked restlessness and confusion. He died two years later as a case of Huntington's Chorea. Case 2.8 presented herself for treatment at the age of thirty-nine, when the history given was that she had for the past three years suffered from choreiform movements, insomnia, and inability to manage her household duties to the satisfaction of her husband. On examination, there was marked chorea of the upper limbs and head and explosive articulation. She has since been admitted to Royal Park Mental Hospital.

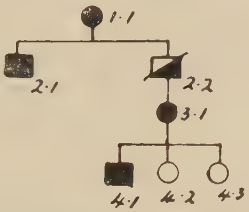
*Family "M"*

Detailed information concerning Cases 1.1, 2.1 and 2.2 of Family "M" is unavailable, except for the fact that all three had suffered from chorea and were insane. Case 3.1 was admitted to the Ballarat Mental Hospital at the age of thirty-seven. It is recorded that the earliest mental symptoms shown consisted of abnormal aggression and maniacal excitement just prior to his admission to hospital, where he died two years later, twelve years after the onset of choreiform movements. His brother (Case 3.2) was admitted to the Bundoora Repatriation Mental Hospital at the age of forty, ten years after the onset of chorea. Mentally he is described as being restless, irritable, aggressive and very depraved in his habits. Death occurred five years later at the age of forty-five.



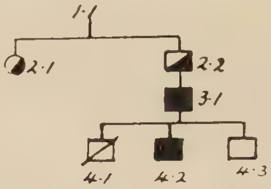
*Family "N"*

Case 1.1 was reported to have had St. Vitus Dance for some years prior to her death in the Kew Mental Hospital some seventy years ago. Details of her clinical history are unavailable, but it is recorded that she had arrived in this country from England some twenty years previously. Her elder son, Case 2.1, as a result of Huntington's Chorea, was admitted at the age of forty to a mental hospital in New South Wales. The younger son was suspected of having committed suicide at an early age. Although no actual chorea was observable prior to his death he was known to be subject to violent outbursts of temper. In the case of his daughter, Case 3.1, who was admitted to the Sunbury Mental Hospital at the age of thirty-five, the clinical notes state that since the age of twenty-eight she had been showing signs of becoming mentally unbalanced. The earliest symptoms shown were paranoid trends and extreme irritability. She eventually became quite incapable of managing her home. Choreiform movements did not become particularly noticeable until several months prior to her admission to hospital. Death occurred at the age of thirty-nine. In the next generation, Case 4.1 began to show signs of chorea at the age of twenty-six whilst he was still in the army. The first symptom was his inability to roll a cigarette. Later, it was noticed that he began to make grunting noises and a year after this began to show unsteadiness in his gait. In spite of the fact that he was drinking heavily, he continued working as a labourer for three years after the onset of his illness before he was eventually admitted to the Repatriation Hospital and later transferred to the Bundoora Repatriation Mental Hospital on account of his mental deterioration. When last heard of his two siblings, Cases 4.2 and 4.3, were in good health and showing no signs of chorea.



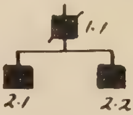
*Family "O"*

The records of this family are still incomplete. Cases 2.1 and 2.2 had both been rather loosely described as being nervy and it is thought that they both possibly suffered from Huntington's Chorea. Case 3.1 developed choreiform movements and irritability at the age of forty and died twelve years later. Case 4.1 was killed in action in World War II. Case 4.2 was discharged from the Army after five years' service, on account of nerves. The earliest symptoms were irritability, irresponsibility, and erotic behaviour, for at least three years prior to the appearance of choreiform movements. He was admitted to Sunbury Mental Hospital at twenty-nine and died ten years later. Case 4.3, who has three children, is apparently normal.



### *Family "P"*

Case 1.1 died at a Mental Hospital from Huntington's Chorea. No other details of this case are available. Of the two children, Case 2.1 began to show signs of chorea at fifty-four, symptoms being clumsiness, fidgety movements, jerkiness in writing, and unsteadiness in gait.

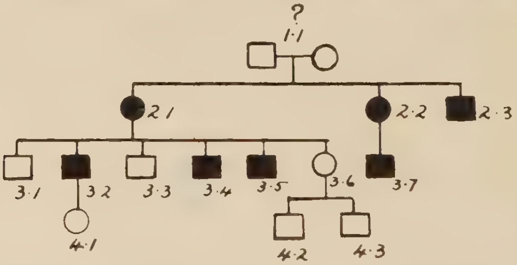


The first mental symptoms, ante-dating chorea for at least two years, were irritability, abusiveness, lack of concentration, and gradual deterioration generally of the higher mental faculties. His brother (Case 2.2) developed chorea at the age of fifty-three. Apart from having no insight into his physical disability, there are as yet no other apparent mental symptoms, and he is still able to carry on his business as a hotel proprietor.

### *Family "Q"*

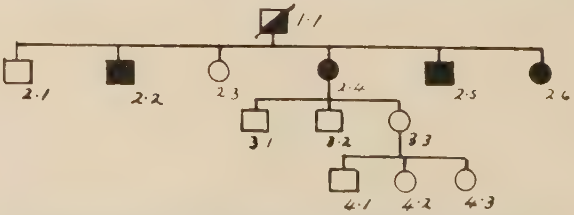
This family includes seven known cases of Huntington's Chorea, but details are only available in the following three cases:

Case 2.1 was admitted to the Ballarat Mental Hospital at the age of forty-six when both dementia and chorea were well advanced. She died five years later. Case 3.4 first showed signs of chorea at forty-five and was admitted to Royal Park eleven years later on account of depression. He died in a benevolent home at the age of fifty-three. Case 3.5 was admitted to Kew Mental Hospital at the age of thirty-seven and was diagnosed originally as a mental defective, no doubt due to his simple dementia associated with infantilism and absence of secondary sexual characteristics. Choreiform movements, which were relatively slight on admission, gradually became more marked, and, at the age of forty-three, when he died, he was grossly choreic.



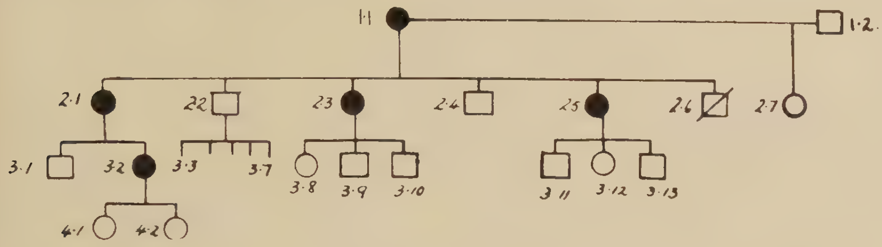
### *Family "R"*

Case 1.1 committed suicide at the age of thirty, and although no factual information is available it is reported that he was probably a case of Huntington's Chorea. Four children are known to have been affected by Huntington's Chorea, although Case 2.4 was the only one admitted to a mental hospital, which was at the age of sixty-two. Signs of chorea had been present since the age of fifty. She was paranoid and mentally enfeebled.



*Family "S"*

Case 1.1, who lived in Scotland and was known to have died of Huntington's Chorea, had six children, the eldest of whom (Case 2.1) migrated to Victoria. Case 1.2, the only known sibling of this generation, is still quite well and is living near Edinburgh. Case 2.1 first showed symptoms of Huntington's Chorea at the age of forty and died fourteen years later. Case 2.2, at present living in Edinburgh, is reported as being quite well. Case 2.3 died of Huntington's Chorea five years ago. Case 2.4, who is living in Bathgate, is reported as being normal. Case 2.5 is at present in the Edinburgh Infirmary suffering from Huntington's Chorea. Case 2.6 died at the age of fourteen.



In the third generation, Case 3.1, at present aged thirty-three years, is reported as being quite normal. Case 3.2, who was recently admitted to Royal Park Receiving House at the age of twenty-seven, suffered from Sydenham's Chorea at the age of seven. On admission to hospital she appeared to be emotionally impoverished and rather indifferent in manner. She had apparently been anergic and neglectful of herself, her children, and her home, and is said to have been extremely irritable and violent towards her family. She was provisionally diagnosed as a schizophrenic, and, although there are as yet no signs of choreiform movements, the probability is that she is an early case of Huntington's Chorea in which mental symptoms have preceded the appearance of chorea.

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# THE EFFECT OF ISONIAZID ON DEPRESSIVE STATES

By

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Isonicotinyl Hydrazide or Isoniazid has for some years now been used in conjunction with other compounds in the treatment of pulmonary tuberculosis. During this treatment certain workers (Robitzek *et al.*, 1952) noted the development of a state of euphoria in their patients. Since Isoniazid was known to exert toxic effects on nervous tissue (Gammen *et al.*, 1953) the hypothesis was made that the substance might be capable of producing an elevation of mood by direct action on the central nervous system. Acting on this hypothesis, Salzer and Lurie (1953) treated a group of patients suffering from various depressive conditions with Isoniazid given orally in the dosage of 50 mgm. t.d.s. for one week. If no toxic effects occurred the dosage was raised to 100 mgm. t.d.s. for a further two weeks, while in a few cases only higher doses were given. These workers maintained this level of dosage in order to avoid the advent of toxic side effects. Their results, which will be discussed later in this paper, led them to the conclusion that isoniazid had a specific therapeutic effect upon certain depressive disorders.

The object of this study, arising out of the work mentioned, was to carry out an initial survey of the effects of isoniazid on the affective component of various depressive states. If any demonstrable therapeutic action had been noted a larger, controlled, and more systematic study would have been undertaken but in view of the results obtained this further project has now been abandoned.

## Study

Thirty-three female patients with various types of depressive states were selected for treatment. As this was essentially a pilot study, no effort was made to select the patients in regard to age or duration of illness, but care was taken to exclude the possibility of organic factors or those pertaining to other psychiatric conditions. The cases of depression selected fell under four diagnostic headings: involutional depression, manic-depressive psychosis, recurrent endogenous depression and senile depression, the second and third categories being separated by the presence or absence of manic phases.

The patients were all interviewed by myself and after a diagnosis had been made were given a routine physical examination. A blood picture was obtained before and after treatment. Isoniazid was given by mouth over a period of three weeks, the dosage being 50 mgm. t.d.s. for the first week and 100 mgm. t.d.s. for the second and third weeks. The patients were then reassessed at interview, and a further follow-up carried out two months later. In some cases a course of E.C.T. was then given, with further follow-up interviews. Patients were assessed after treatment as being unchanged, improved, or recovered.

During the isoniazid therapy no other treatment was given except for symptomatic remedies, including nocturnal sedation when needed. As in no case were any toxic effects noted, these will not be alluded to in the results.

In no case was the treatment found to be unpleasant, so that its management was simple and uneventful. No consistent trend either upwards or downwards was noted in the patients' weight after treatment.

## RESULTS

These are summarized below in Table I.

TABLE I

| Diagnosis | No. of Patients | No. of Recoveries | | No. of Improvements | | Total |
|---|---|---|---|---|---|---|
| | | Immediate | Within Two Months | Immediate | Within Two Months | |
| Involutional Depression .. | 17 | – | – | 1 | – | 1 |
| Manic Depressive Psychosis | 5 | – | – | – | 2 | 2 |
| Recurrent Endogenous Depression .. .. | 7 | 1 | – | – | 1 | 2 |
| Senile Depression .. .. | 4 | – | – | – | – | – |
| Total .. .. .. | 33 | 1 | – | 1 | 3 | 5 |

It can be seen that from a total group of thirty-three patients given the treatment, one patient recovered immediately, one improved immediately, while three others improved within two months of finishing the isoniazid therapy.

These results have been further tabulated above under diagnostic headings which will be discussed below. In all, five out of thirty-three patients given the treatment showed some degree of clinical improvement. This figure in itself is very small and might well be accounted for by chance spontaneous improvement, and in order to examine further the latter possibility brief summaries of these five cases are appended so that the significance of their improvements can be further assessed:

*Case 1.* Miss B.S., aged 50 was admitted to Cane Hill Hospital on 26.3.54 complaining of depressive symptoms of several weeks duration. In November, 1946 she had been treated for a few weeks in West Park Hospital for a depressive state. At that time she was mute and retarded, but she made a rapid spontaneous recovery and was discharged the following month. On admission to Cane Hill the patient was depressed and anxious, displayed psychomotor retardation and suffered from insomnia. A diagnosis of recurrent endogenous depression was made and isoniazid therapy commenced on 7.4.54, finishing on 28.4.54. The patient was still slightly tense and depressed but became symptom-free during the following week. She was discharged on 21.5.54 and had remained symptom-free up to 22.7.54 when she was seen as an out-patient for follow-up purposes.

*Case 2.* Mrs. M.L., aged 61 was admitted to Cane Hill on 27.1.54 with a history of four weeks depression, She had previously become depressed in October, 1951 and had remained so until her admission to Cane Hill in January 1953. At that time she was given six E.C.T., made a rapid recovery, and was discharged in February, 1953. She relapsed the following June, was readmitted to Cane Hill and given a course of eight E.C.T. She again recovered and was discharged in August, 1953. On the present admission she was depressed, retarded, harboured delusions of guilt and complained of insomnia. A diagnosis of Involutional Depression was made and a course of isoniazid was given between 6.2.54–27.2.54. At this time the patient was well except for a mild degree of subjective depression, but by 1.5.54 she had relapsed with severe depression, anxiety and insomnia.

*Case 3.* Mrs. I.M., aged 31 was admitted to Cane Hill on 28.11.52 with a history of elation and hyperactivity of a few weeks duration. At the age of 16 she had been admitted to the Maudsley Hospital with depressive symptoms. While there she recovered rapidly but relapsed and was transferred to St. Ebbas' Hospital where she made a rapid recovery. The patient continued to have numerous mild episodes of mania and depression until her present admission. At this time she was elated and overactive, and a diagnosis of manic depressive psychosis—manic phase—was made. Following two E.C.T. the patient improved but remained hypomanic until a sudden change to normality in March, 1953. The following month she became depressed; in July she was given three E.C.T. with no effect. During the following month a course of "artificial hibernation" was given, also with no effect, and in October, 1953 she was noted to be depressed, suicidal, and having delusions of guilt. A course of isoniazid was given from 16.10.53–6.11.53 with no immediate effect, but by January, 1954 the patient had improved though she was still slightly depressed and tense. In February, 1954 a course of five E.C.T. was given with no effect and the patient remained unchanged up to the following May.

*Case 4.* Miss L.V.H., aged 33 was admitted to Cane Hill on 13.11.53 with a history of depression with obsessional features over a period of five months, there having been no previous episodes. On admission she was severely depressed and retarded, with considerable obsessional anxiety. A diagnosis of Endogenous Depression was made and isoniazid was given from 16.11.53 to 4.12.53 with no immediate effect, but during the following weeks the patient made a gradual improvement and was discharged on 3.1.54 with residual symptoms. On 9.3.54 she was seen at out-patients but had relapsed, though still managing to work.

*Case 5.* Mrs. E.E., aged 65 was admitted to Cane Hill on 22.4.54 suffering from depressive symptoms of a few weeks duration. In 1920 after her mother's death she was treated for depression and mania for seven months in the Bethlem Royal Hospital. She then remained well until her husband's death in 1943 when she became acutely depressed; she was admitted to Cane Hill where she was given four E.C.T. and discharged recovered after two months. In 1951 she was again admitted to Cane Hill following a sudden recurrence of depressive symptoms. She recovered after six E.C.T. but relapsed quickly. In January, 1952 after a further three E.C.T. she was discharged recovered. In May, 1952 she again relapsed and was admitted to Cane Hill. She recovered completely after five E.C.T. and remained well until her discharge the following October. She then relapsed immediately and was readmitted when she made a gradual recovery until her discharge in August, 1953. On the present admission she was depressed, agitated and hypochondriacal and a diagnosis of Manic Depressive Psychosis—depressive phase—was made. Isoniazid therapy was given from 3.5.54 to 24.5.54 with no effect, but by July she was noted to be much less depressed and anxious, more active and sleeping better.

The majority of patients, as has been stated, did not show any clinical improvement from isoniazid therapy. As it might be argued that many of these patients would not have improved with any other treatment, those previously or subsequently treated with E.C.T. are enumerated below in Table II.

TABLE II

| Diagnosis | No. of Patients | No. of Patients Previously Recovered or Improved by E.C.T. | No. of Patients Subsequently Recovered or Improved by E.C.T. |
|---|---|---|---|
| Involutional Depression .. .. | 16 | 6 | 5 |
| Manic Depressive Psychosis .. | 3 | 2 | 1 |
| Recurrent Endogenous Depression | 5 | 2 | 2 |
| Senile Depression .. .. .. | 4 | 2 | 0 |
| Total .. .. .. | 28 | 12 | 8 |

From Table II above it can be seen that among the twenty-eight patients unaffected by isoniazid, twelve had previously improved after E.C.T. while eight subsequently improved with this treatment.

## DISCUSSION OF RESULTS

From a total group of thirty-three patients suffering from depressive states, five improved to some extent after isoniazid therapy. Brief histories of these five cases have been outlined, from which it can be seen that in Cases 2, 3 and 5, isoniazid produced clinical results inferior to those previously effected spontaneously or by E.C.T. In Case 1 the effect of isoniazid was approximately equal to that previously attained without specific treatment, while in Case 4 no comparisons can be made. In none of these cases therefore can isoniazid be shown to be superior to no treatment at all while in three of the five cases it would appear to have been less effective than E.C.T. given previously.

This apparent superiority of E.C.T. over isoniazid is also reflected in those cases not improved by the latter, over half of whom had either previously or subsequently been benefited by E.C.T. It is interesting to note that the superiority of E.C.T. over isoniazid is least manifest amongst the cases of manic-depressive psychosis in whom the tendency for spontaneous remissions is great, but in the other diagnostic groups, in whom this tendency is less marked, the superiority of E.C.T. over isoniazid is obvious, even in those patients suffering from senile depression.

In conclusion it may be stated that from this study there is no evidence that isoniazid has any therapeutic effect upon depressive states, and furthermore, that if it has any such effect this is markedly inferior to that of E.C.T.

## General Discussion

These findings do not agree with those of Salzer and Lurie, whose results are appended:

| Diagnosis | No. of Cases | No. Improved |
|---|---|---|
| Agitated Depression | 12 | 8 |
| Psychoneurotic Depression | 17 | 11 |
| Manic Depressive Psychosis | 11 | 8 |
| Anxiety Neurosis | 1 | 1 |
| Total | 41 | 28 |

Differences in selection may in some degree explain this discrepancy. Salzer and Lurie treated cases of anxiety neurosis and psychoneurotic depression which were not included in this study, and none of their other cases were severely depressed or suicidal. In spite of these differences in selection there remains a marked discrepancy between the results obtained by these authors in their groups of patients with agitated depression and manic depressive psychosis and those obtained in this study. Since none of Salzer's and Lurie's patients were severely depressed, however, it is possible that factors other than isoniazid may have accounted for the improvements noted.

The negative results from this study are in agreement with those obtained by other workers. Wilson (1953) in a series of non-tuberculous patients with depressive disorders found isoniazid to have no therapeutic effect. Hunt and Wassersug (1953) treated a group of tuberculous patients who were also schizophrenic and concluded that isoniazid only produced euphoria as a concomitant of its beneficial effect upon the tuberculous process, and this conclusion was also obtained by Bennett *et al.* (1954) in a series of chronic schizophrenic patients.

It is interesting to note that in this study isoniazid was not associated with any constant increase in weight. Since the anorexia associated with depressive symptoms was in only a few cases improved, this finding is hardly surprising. It indicates that isoniazid has no inherent tonic effect, a conclusion consistent with the finding of Silverman (1954) who in a comparison of the effects of Isoniazid and Modified Insulin Therapy in matched groups of psychoneurotics, found the former to produce no increase in weight while in the latter treatment a consistent rise was recorded in most cases.

No toxic effects were noted amongst the patients in this study, but this was anticipated by keeping the dosage under 300 mgm. per day (Gammen *et al.*, 1953).

## Summary

(1) A group of thirty-three patients suffering from depressive states were treated with isoniazid over a period of three weeks.

(2) No evidence of clinical improvement attributable to the isoniazid therapy was found.

(3) Evidence was adduced in a number of patients that E.C.T. was greatly superior to isoniazid in the treatment of depression.

(4) No increase in weight nor toxic effects were associated with the isoniazid treatment involving doses of less than 300 mgm. per day.

(5) These results were discussed in the light of recent work.

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# LILLIPUTIAN HALLUCINATIONS

## EIGHT ILLUSTRATIVE CASE HISTORIES

By

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*From Runwell Hospital*

Raoul Leroy was the first alienist to take a scientific interest in diminutive hallucinations which he labelled "Lilliputian" (1909) and they can best be described in his own words (1922).

> "It is the vision of small people, men and women of minute and slightly variable height; either above or accompanied by small animals or small objects all relatively proportionate in size. . . . These hallucinations are mobile, coloured, generally multiple . . . All this little world, clothed generally in bright colours, walks, runs, plays and works in relief and perspective."

He further stated that these visions were accompanied by a pleasurable state of mind, in contrast with the more toxic hallucinations, such as are found in acute alcoholic poisoning, which can be terrifying to the beholder. Leroy pointed out that the affective state rules the character of the hallucinations. For, in the rare cases in his experience where the visions were painful, the figures were black. In a very few of his cases the visions were matched by hallucinatory voices which assumed a Lilliputian tone. He made a clear distinction between micropsy, where the normal environs are seen in miniature, and Lilliputian hallucinations where this is never the case, and stated that he had never seen a combination of the two.

According to Savitsky *et al.* (1941) Lilliputian hallucinations have been described as occurring during the course of measles, erysipelas, typhoid fever, cholera, chorea and sepsis; in acute and chronic alcoholism; in cocaine, caffeine, haschisch, hyoscine and atropine poisoning; in general paresis, chronic encephalitis, parieto-temporal and temporo-sphenoidal tumours and vascular lesions of the occipital lobe; in the aged and cerebral arteriosclerotic; in hypnagogic states, blindness, schizophrenia, epileptic aura and in hysteria. They reported that Leuret was the first to describe them in 1834 and that Sauve in 1847 was the first to use the term, "Lilliputian". Yawger (1925) stated that the first description of such hallucinations was given by Macarius in the fourth century A.D., who wrote that many little black creatures were playing unseemly pranks on some of the priests.

Conklin (1925) cited the peculiar case of a man who claimed to be able to conjure up at will visions of panoramic scenes and Lilliputian people. He attempted to photograph them and misinterpreted slight blotches on the film as being the images of his Lilliputians. Alexander (1926) described the case of a schizophrenic woman whose twenty years in an asylum were spent in protecting some tiny Lilliputian children. He wrote:

> "I have often asked her to put some of the children into my hands but evidently she lacks confidence in me, because she has never complied with my wish. On occasions I have picked them off her lap, but always incurred displeasure by this action."

Angyal (1936) discoursed on the differences between the Lilliputian hallucinations of schizophrenics and of the sane. In the former they are hazy, ill-defined and appear to emanate from the bodies of the patients.

Thomas and Fleming (1934) gave an account of an arteriosclerotic patient with some degree of uraemia due to an enlarged prostate who had, in addition to Lilliputian hallucinations, a vision of a dog eight feet (2·4 metres) long. This they called a "Brobdingnagian hallucination", in deference to Swift. In a series of 106 cases with delirium and allied states collected by Wolff and Curran (1935), 72 had visual hallucinations and of these 10 had Lilliputian and/or Brobdingnagian hallucinations. Four of these were alcoholics, two epileptics, one had cardiac failure, one had a fever of unknown origin, one chorea and one an exophthalmic goitre. This is probably the largest series of cases of Lilliputian hallucinations described in the literature.

In the last decade or so articles on this subject have become rare. In 1952 Michaux and Roger described a young girl of eight years suffering from epilepsy who was found to have bilateral temporo-occipital foci on EEG. She saw Lilliputian folk whilst unconscious and could recall and describe their antics afterwards. Todd (1954) gave an account of a man with trichlorethylene poisoning who had microptic illusions which the author mistakenly calls Lilliputian; and Wyers (1954) made the same mistake about two cases suffering from methyl bromide poisoning.

The case abstracts of eight patients are presented below. They illustrate the diversity of aetiological factors involved, but there appear to be features common to all.

### *Case 1*

A retired cashier of 77, was first referred to the psychiatric out-patient clinic in April, 1952, because he complained that some strange people were haunting his house, and directing gas fumes against him. These people had been present since the previous Christmas in the form of dummies; they were directed by human agents and were attempting to steal his possessions. He could smell the fumes which had been introduced into his house in an attempt to kill him.

There was no significant factor in his family history or his early life. He had been married for over 50 years and complained that his wife domineered the house. There had been two children of the marriage but both had died in infancy. Before he retired ten years ago he had been a heavy drinker but he seldom drank now. He and his wife lived alone in a bungalow in a quiet rural area of Essex, having for company little more than their television set. He was reckoned by his wife to be a bit of a crank, bad tempered and irritable. The couple lived on a small private pension of the wife's which would cease at her death. The patient was afraid that he would be left destitute if his wife should die, which was a possibility to be reckoned with, as she was a cardiac invalid.

Physically the patient was typically pyknic and little over five feet (156 cm.) tall. He had osteoarthritis of most of his large joints and evidence of arteriosclerosis with mild hypertension. At interview he gave the impression of being a pleasant old man, polite, well-mannered and willing to discuss the weather and the intricacies of gardening as readily as his own complaints. Apart from his systematized delusional complex he was rational, correctly orientated and had a fairly intact memory considering his age, but inclined to be forgetful for recent events. His intellect was normal and his personality well preserved.

At the first interview he gave an account of having seen little soldiers marching through his bedroom wall, and of a policeman who followed him from room to room. He also had heard voices making such remarks as, "murder or suicide" and, "dead men tell no tales". Over the following year he was treated with fairly large doses of a vitamin B complex and nicotinamide, and he was seen regularly at out-patients. Gradually his hallucinations became less intense and then practically disappeared and he became willing to believe that they were unreal. Finally he no longer wished to admit that he had ever seen anything unusual and he stopped taking his tablets. Then, at the beginning of 1954 his hallucinations started to reappear. By June, 1954 they became practically continuous despite a further course of vitamin B therapy. He was now depressed and was easily irritated and tired. However his personality and intellect remained unimpaired. His wife reported that he often spoke to the small people that plagued him and became indignant with her when she denied being able to see them. Recently he gave the following account of his peculiar world.

In his house, in his garden and, indeed, everywhere he goes and at all times of the day and night but especially in the early mornings he sees men, women, children and all sorts of animals including donkeys, cows and stags. They are all about six inches (15 cm.) high but some of the people walk on stilts which increases their stature to between five and six feet (150–180 cm.). The "humans" are dressed in a green leaf uniform; the men are mostly bald but the women have hair of all colours. Their faces are a dark grey or blackened and they look "as ugly as sin". Sometimes they wear the masks of animals. A few of them talk sensibly on ordinary every day events but they will not answer him when he speaks to them. They frequently laugh. He is more annoyed by them than amused or frightened, despite the fact that they sometimes threaten him. If this should happen he has only to mention the local policeman and they run off up the street but, if he should talk of the sanitary inspector, they show no concern. They just stand and stare at him but one has gone as far as to prod him. They climb trees like monkeys. They made holes in the walls of his house. They once turned on the water and made baths, and then jumped in with their clothes on and the water ran through into his property. He complained to the local water-board about that. Recently the little people have taken to throwing powder about, so that now he has a sore throat.

An EEG tracing was made in September, 1954 and this showed generalized slow activity at 5–6 c/sec.

*Case 2*

A Dutch widow of 69 first came to the out-patient clinic in September, 1954, complaining that a host of little people had invaded her house and garden, much to her annoyance. She asked whether anything could be done to get rid of them. She wrote to the town council, but they would not help her.

The patient was left an orphan at the age of 14 and came to this country when 16. When 23 she married a man about twenty years older than herself but he was killed three years later. She was childless and for many years had lived with a lady friend. During the last three months she became rather anergic and easily tired.

She was about five feet (156 cm.) tall with a broad rotund figure and a red face. She had peripheral and retinal arteriosclerosis and her B.P. was 170/90. She was obviously rather depressed, agitated and much preoccupied by her visual hallucinations. Her memory for recent events and ability to recall were very poor but, apart from this, she had a well preserved personality and intellect, and was well able to conduct a rational conversation on a neutral topic. She gave the following account of her troubles.

A male neighbour asked her to rent a part of her garden to him, and against her better judgment, she agreed. He then directed a lot of small people into her home and garden to annoy her. They appeared at all hours, but were mainly to be seen at dusk and at night. She saw men, women and children who were about one foot (30 cm.) tall and a "head man" who was about four feet (120 cm.) tall. The day before coming to the clinic she saw a man about nine feet (270 cm.) tall in her bedroom but he ran away when she called out for help. They dressed in ordinary clothes of dull colours but she once saw some dressed colourfully "in the old Parisian fashion". There were a few pretty little blonde girls of whom she was very fond, but mostly they were ugly with dark hair and black beards, and these frightened and annoyed her. They painted their faces either red or white. They conspired together in whispers and carried messages all over the town. Only once did she hear what they were saying, and that was a threat to murder her. They will not answer her questions but respond by laughing at her. At the orders of their "head man" they dug a huge hole under her bedroom and fitted it out as a canteen and a sitting room, nicely furnished with normal sized furniture. At night they put up a black screen in the garden and roost in the trees. She does not like the "head man" for he is rather brutal. If any of the others annoy him he breaks them up just like sticks and buries them in holes in the garden. She has become very concerned just lately, as the small people seem to be growing rapidly in number. Although they do not steal or do any real harm, she is afraid that they will overrun the world and frighten the people.

She was put on a vitamin B complex and nicotinamide. After one week she reported that she was more cheerful and less worried about her little people. An EEG was done and showed 5–6 c/sec. activity.

*Case 3*

This was a widowed lady of 70 years who was first referred to the psychiatric out-patient clinic in September, 1953. Her family and early history were normal. She married when 24 but, a few years later, her husband was killed. The one child of the marriage died in infancy. She did not remarry but stayed with a younger sister who went out to work and, for the last sixteen years, with a man who was ostensibly the lodger. In recent years she had become very deaf, so that, even with a hearing aid, she could only hear with difficulty. Her sister described her as being a mischief-maker and a great one for scandal.

The history of her illness was that, over the last year or two, her man had started to neglect her in favour of his own niece for whom he had grown fond and this had come to a head last month when he struck the patient. The patient misidentified her own image in mirrors for that of this niece. She was amnesic and confused and was evidently suffering from early arteriosclerotic dementia. She was prescribed large doses of a vitamin B compound and improved considerably. In June, 1954 she was re-referred because she was incapable of doing her housework and wandered sleepless during the night.

Her "lodger" had left her in April, 1954 to go to live with his niece and, since then, the patient had deteriorated. She saw the niece's face in all the mirrors (which her sister now kept covered), and in the windows one of which she had smashed in a rage. She was anorexic and physically weakened. She had little memory for recent events and had started to neglect her dress and toilet. Over the next two months she was given large doses of nicotinamide, and improved, in that she had more rapport with her surroundings, was now capable of looking after her personal needs and helping with the housework. It was only in July, 1954 that she first mentioned the small people.

Her little people were about six inches (15 cm.) high, and they appeared in her house mainly during the day when she was alone. However, she had seen them at other times, and in other people's houses. Most of them were women and were dressed in brightly coloured frocks. Sometimes they stood on the window-sill and stared at her; at other times they danced in front of her. She was not frightened by them but only amused, and she was quite certain that they were real. Sometimes they would annoy her and then she would chase them away.

*Case 4*

A married man of 55, with one son and no particular family or personal history, was admitted to Runwell Hospital in January, 1952. Four weeks before his admission he retired to bed with an influenza-like illness. The next day he jumped around in his bedroom trying to swat imaginary wasps. In the night he complained that there were four men in his room who were attempting to pour petrol over his wife. Subsequently pneumonia was diagnosed and he was given a course of sulphonamides and penicillin. One evening he described how a host of little men in his room were putting wires all over the ceiling, and the following day he was observed to be instructing his little men in their task. He became more confused and disorientated during the next few days, so that eventually he no longer recognized his own house. It was in this state that he was admitted.

His pre-morbid personality was described as friendly and cheerful, good hearted but a little reserved. In his work as a plumber he was said to be honest, trustworthy and tenacious. He did not drink. His hobby was to make children's toys. Physically he was of medium height, athletic build but underweight. He had a low-grade temperature and a raised E.S.R. An X-ray of chest revealed a large left upper lobe cavity with a fluid level.

He gave the following account of himself. The "Peculiar People" had been trying to persuade him to marry a young girl, in order to distract his attention whilst they robbed two adjoining houses of their timber. He would not dream of deserting his wife, and refused their offer. In revenge they sent small men three inches (8 cm.) high into his house where they interfered with everything, especially the electric light. They played about his room and sometimes camouflaged themselves into a brick wall. He said that the "Peculiar People" made small men and animals out of plastic material and directed their movements. They injected them with hormones, and taught them to act like normal animals. He had seen little dogs run around like ordinary dogs. These little men took down his electric light and fitted up a wheel with a cutting edge in its place. This was turned by a motor, and was a danger to everybody. He managed to break the spindle joining the wheel to the motor so that the contraption would not work. Another of their activities was to take the floor joists and planks away from the house next door, and he could hear them chopping up the wood all night.

Apart from his hallucinations, the patient was quite rational, whilst he was in hospital. His stream of talk was rapid, coherent and logical for neutral subjects. His affect was appropriate. A week after his admission he reported seeing a troupe of cats, varying in height from 4 feet (120 cm.) to 3 inches (8 cm.) walking in the hospital grounds. He also saw processions like pageants, where all the small people were dressed up in period clothes. One man had on the helmet of a knight in armour and one side of his moustache was curled up and the other side down.

An EEG showed that the dominant activity was theta at 6–7 c/sec. This was bilateral and occasionally came in short bursts mixed with delta at 2–3 c/sec. It was maximal on the left and in the fronto-temporal region but there was no consistent localization by phase reversal. It was considered that the record was compatible with cerebral arteriosclerosis but, because of the marked laterality of the dominant activity, an organic condition could not be excluded.

The patient was transferred to another hospital for bronchoscopic examination and treatment. A few months later a lung resection was performed for carcinoma, but the patient eventually died.

*Case 5*

A married man of 56 with one daughter, a tobacconist by trade, was admitted to Runwell Hospital in December, 1952 because of delirium. For the past four years he had suffered from intermittent attacks of bronchitis and asthma, which were progressively becoming more severe, in line with an increasing obesity. A few days before admission he had retired to bed with a particularly severe attack and, in the night, had become restless, confused and delirious.

He had led a normal enough life and his pre-morbid personality was described by his wife as quiet and uncommunicative at home but effusive and ingratiating at his business. He was extremely conscientious and obsessional in his work; he was honourable and honest, obstinate and unrelenting. As a husband he was considerate and affectionate but not demonstrative.

On admission his temperature was slightly elevated. He had a barrel-shaped, emphysematous chest with evidence of broncho-pneumonia confirmed by an X-ray of his chest. His B.P. was 160/100; he was extremely dyspnoeic and cyanotic and was obviously very toxic. Mentally he was well orientated, with intact memory and personality. He said that before his admission to hospital he had heard disembodied voices, and had seen bright lights. He described seeing a panoramic and vivid vision of little people playing on the seashore. Whilst in hospital he had hallucinations during the night of small, brightly coloured men like dwarfs who hopped around and over him on the bed. They were faintly amusing, albeit frightening at times, and he was ashamed to discuss them during the day.

The patient was treated with sulphonamides and penicillin, and made a good recovery. In 1953 he had pneumonia, but there was no recurrence of hallucinations.

*Case 6*

This was a married man of 64 who was admitted to Runwell Hospital in April, 1953. He had been happily married for thirty years and had two children. There was no significant family history and he had a normal upbringing. In the first world war he lost his right arm. He was described by his wife as a happy, easy going, even tempered, kind and thoughtful man who mixed easily. He was a non-drinker.

In 1951 acromegaly and Parkinson's disease were diagnosed, and he was prescribed Artane, which he continued to take up till his admission. For the past two months he had complained that midges, bugs and maggots were crawling all over his clothes, over the tablecloth, on his arms and under his tongue, and were causing him considerable distress. He frequently asked his wife to brush them away for him. He also saw a little Lilliputian man who came to him at night and amused him.

Immediately following withdrawal of Artane he became very much brighter and was no longer hallucinated. However, following this, he developed a mildly depressive and paranoid reaction which necessitated his stay in a hospital for some months.

*Case 7*

A single woman of 54 was admitted to Runwell Hospital in February, 1953, because of what was thought to be psychomotor epilepsy. There was no significant family history and her early upbringing was normal. She had been a cook-general, holding one post for twenty years. She had a duodenal ulcer removed in 1935, a thyroidectomy in 1940, and a hysterectomy in 1946. In December, 1950, she suddenly developed Jacksonian fits and became unconscious for twenty-four hours. Following admission to hospital she had a haematoma of the right cerebral hemisphere drained, made an excellent recovery, and returned to work for six months. She then complained of nervousness, and left her job for the protection of her sister's home. Over the next eighteen months she steadily deteriorated. She became disinterested, lethargic and sometimes drowsy. She would do no work, and often lay in bed all day. Occasionally she was incontinent. Her only occupation was to talk incessantly of her illnesses. She complained of feelings of unreality, of frontal headaches, that her memory was poor, of paraesthesia of her limbs and of a coal-gas like smell. On admission she was found to have residual signs of a left hemiplegia. She recounted how she saw little men about three inches (8 cm.) high sitting on her bed at night. Their faces were white and they were dressed like ordinary people in dark clothes. They never moved or talked, and she was neither amused nor frightened by them. She only saw them over a period of two to three weeks.

In hospital she developed "absences" in which her face went blank in the middle of a sentence and her left arm became abducted. She had an aura which consisted of a sinking feeling in the pit of her stomach and a burning smell at the back of her throat. An air encephalogram showed a dilated left lateral ventricle with a distorted anterior pole. An EEG tracing showed continuous high voltage spikes over the whole of the right hemisphere with phase reversal occurring most commonly in the right posterior temporal and right frontal areas.

*Case 8*

A 35 year old married woman with two children was first seen in the psychiatric outpatient clinic in July, 1954. There was no relevant family history and her childhood and youth were normal. She had been happily married for eight years and her health was good. She was described as a cheerful person but quick tempered. She did not drink.

She said that for the last eight years she had not felt well. When walking in the street the traffic seemed to come straight towards her, and sometimes when walking up stairs, they appeared to come up to meet her. She suffered from constant frontal headaches. For the last three months, when lying in bed by day or night, she sometimes saw diminutive figures coming out of holes to stand and stare at her. They were white, had no faces or hair and were just like pieces of paper. Once or twice she had seen a little man in a trilby hat knocking on her window just as she was falling asleep. This only lasted a few seconds and was in the nature of a hypnagogic hallucination. She realized that they were not real. Since the age of 17 she occasionally had the presentiment that someone was looking over her right shoulder and, during the last four months, this had become more frequent and was now over both shoulders.

The resting level of an EEG was normal but, on photic stimulation, the record became grossly but non-specifically abnormal; myoclonic twitching of her face and limbs occurred, and she had the presentiment of someone standing on her right side.

## DISCUSSION

The case histories presented here amply illustrate the fact that Lilliputian hallucinations form a symptom-complex, being associated with emotional feeling, ideas of reference and auditory and olfactory hallucinations. The visual hallucinations are found complicating a variety of illnesses and are not necessarily of psychotic significance, even although they may be accompanied by a conviction of their reality. The hallucinations of the first three cases described appeared in a cerebral arteriosclerotic setting; there was also evidence of early dementia and, as will be shown later, of paranoia. Those in cases 4 and 5 appeared in toxic delusional states where the toxins were endogenous and where there was the additional factor present of cerebral anoxaemia. At some period of their illnesses there was also confusion and disorientation. The delirium in Case 6 was due to an exogenous toxin but paranoid and depressive symptoms later became evident. The illnesses present in Cases 7 and 8 were almost certainly of an epileptogenic nature and the Lilliputian hallucinations formed only a part of the malady.

Judging by the paucity of cases reported in the literature, Lilliputian hallucinations are an extremely rare phenomena. The causal factor in the great majority of those reported was a toxin, either endogenous or exogenous, and next in frequency were those associated with cerebral tumour and epilepsy. Lilliputian hallucinations occurring in the course of cerebral arteriosclerosis was last reported in 1934 (Thomas and Fleming) which makes it rather remarkable that three of the eight cases described above were in this group. A feature of these three patients was the great length of time over which they have experienced their hallucinations. Case 1 has been entertained by his for over two years. Lilliputian hallucinations complicating a respiratory illness, as occurred in Cases 4 and 5, has only once before been reported in the English language literature (Fleming, 1923). Case 6 is unique in that there has been no previous report published inculpating "Artane" as the cause of a delirium with Lilliputian hallucinations. However, it is remotely possible that this man's acromegaly and Parkinson's syndrome may also have been precipitating factors. Critchley (1939) reports that a syndrome of mild confusion and persistent visual hallucinations is seen in cases of pituitary and juxta-pituitary tumours and in chronic epidemic encephalitis. Cases 7 and 8 bring to mind the woman described by Beevor and Jackson (1889) who saw, as part of the aura of her fits, a little black lady busily cooking. Whereas in their case a large anterior temporal lobe tumour was discovered at autopsy, in the two cases described here no evidence of a tumour has yet been found. It is usually accepted that visual hallucinations are of doubtful value in the localization of cerebral tumours (Cairns, 1939). The hallucinations of Case 8, however, are very much like those said to be produced by stimulation of Brodmann area 18 of the cerebral cortex (Wagener, 1948).

Scrutinizing the histories presented here, it is seen that there are many points of similarity in the hallucinatory form and content of the first six cases, and especially of the first four. The last two, grouped together as epileptogenic, differ in that the figures seen were less elaborate (or more elementary) and had neither colour nor movement. The visual hallucinations of the others, however, were more elaborate, some amazingly so, and they were incorporated into the environment of the patients. They had colour, movement and variety, and several were combined with olfactory and auditory hallucinations. One patient also suffered from haptic hallucinations. They engendered strong emotional feeling which was frequently of an ambivalent nature. Thus the patient was sometimes amused by their small intriguing figures, yet, at other times, he was frightened by their menacing giant-size or behaviour. He was charmed by their prettiness or revolted by their ugliness; he was attracted by their bright clothes or repelled by their drabness, and he felt sympathy for their plight or was annoyed by their stares.

This ambivalency indicates a conflict which has been repressed but, under the stress of an illness or cerebral degenerative process, threatens to break through to consciousness. The ego defends itself against this threat and there is displacement of the accompanying ambivalent affect on to the small figures; which themselves are probably the projected symbols of the suppressed conflict.

The nature of this conflict in Case 1 is probably to be found in the patient's relationship with his wife on whom he was dependent financially, much to his disgust. He often complained of her nagging nature and spoke of her ill-health with some feeling, as being a great burden to them both. In Case 2, considering that the woman's imagined provocateur was a male neighbour, it may be presumed that her conflict was over a long-felt need for male company and protection, and perhaps too, over her thwarted maternal instincts. The precipitation of conflict in Case 3 was the poor woman's desertion in her old age. She desired her quota of revenge and companionship from the same man. The ideas of reference expressed by patient 4 about the Peculiar People trying to force him to marry a young girl, may have been a distortion of a phantasy or of a true life situation. In either case the ideas represent a repressed conflict. In Cases 5 and 6 the actual conflict is difficult to discern. It is possible that it was more historical and "played out" in these cases and had no reference to their present situation. It could be that it was the fortuitous unearthing of an old complex, especially as there was little affect accompanying their hallucinations which, in addition, were of a mildly pleasant nature.

The delusions were also frequently associated with other paranoid symptoms, such as suspiciousness and ideas of reference of a persecutory nature, often in a depressive setting. The patients themselves had well-preserved personalities such as are usually found in the paranoid reaction types and, like the latter, had their moments of grandeur, in their case, when comparing themselves with the diminutive size of their creations. The toxic cases were obsessional, hard-working, conscientious people, inclined to worry and to set high standards for themselves. Hence they provided ideal material for ambivalency.

For these reasons it is suggested that the Lilliputian hallucination symptom-complex can, in most cases, only occur in a patient predisposed by paranoid personality traits and suffering from a conflict in disequilibrium. The less clouding of consciousness there is in the patient, the stronger must be his paranoid tendencies—his ability to project and to form symbols; but never so strong as to precipitate a delusional illness without the presence of some organic factor. In the patients described here justice is being enacted, not, as in the paranoid states, by a process of self-exaltation, but by the degradation of the symbols of their conflict. Thus they see people the size of a Tom Thumb whom they can domineer and even chase away. The patients always triumph, if only temporarily, and they gain a feeling of power—of being like Gulliver. Their equilibrium is re-established.

The form and content of the hallucinations is also dependent on the environmental stimuli present and on the individual equipment and experience of the patient. Wolff and Curran (1935), in a paper on the nature of delirium, state that these factors are more important than the toxic precipitating factors of the delirium, and their conclusion appears to apply to the arteriosclerotic as well as the toxic patients described in this paper. Thus, in all the arteriosclerotic patients, illusions were frequently the starting point for an hallucination. For instance, a stick was misidentified for a small figure and a clock for a face. The small element of dementia present led to a tendency to confabulate.

The small folk also fulfilled a long-felt need of these old, childless, lonely people for the company of children. In Case 4 one can detect the influence of the man's job as a plumber and his hobby as a toy-maker, in the nature of his hallucinations. In Cases 5 and 6 the particular form which their hallucinations took may have been the result of a desire to dominate for a change. The subservient man was having his day as the master.

There have been very few attempts made at explaining the occurrence of Lilliputian hallucinations. Alexander (1926) based her theory on Adlerian premises. She thought that patients gain a feeling of strength and power by visualizing small people, as they themselves suffered from an inferiority complex. Conklin (1926) offered an explanation along more physiological lines. He postulated a reversion on the patient to a stage where the constancy of magnitude of perception was imperfect, permitting the occurrence of images of diminutive size, culled from experiences prior to the development of this constancy of magnitude. It is very doubtful whether patients could have had many experiences before a constancy of magnitude was established, and it is more likely that this is an explanation, not of Lilliputian hallucinations, but of micropsy.

## Summary

A brief review of the literature of Lilliputian hallucinations is given and eight new cases are described. These have been separated into arteriosclerotic, toxic and epileptogenic groups. A theory is put forward that there is a Lilliputian hallucination symptom-complex which, apart from those cases due to an epileptic focus or cerebral tumour, can only be precipitated in a patient with paranoid personality traits, plus an unresolved unconscious conflict. Mention is made of previous theories on this subject.

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# ELECTRICAL TREATMENT OF ANXIETY STATES

By

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DURING the past five years a number of reports have acclaimed Subconvulsive Electrostimulation as a therapeutic measure for the relief of states of anxiety and tension. In general, these accounts have proved unconvincing, since the authors have seldom provided either controls or even details of their results. The report of Hargrove, Bennett and Ford (1953) has been the only exception to both of these criticisms—and the only adverse account. The present investigation was therefore conducted as a "blind" trial in order to provide an unbiassed evaluation of the subject. The series comprised 100 patients, half of whom received the electrical treatment while the other half were subjected to a control procedure. Objective evidence was furnished by psychometric tests. An autonomic test of reputed prognostic significance, and a follow-up study, were also included.

## HISTORICAL SURVEY

Hirschfeld (1949), who developed the application of Subconvulsive Electrostimulation under pentothal anaesthesia, first reported, and later confirmed (Hirschfeld, 1950, 1953; Hirschfeld and Bell, 1951), good results with this form of treatment in anxiety-tension states. At the same time, and independently, Alexander (1950) used subconvulsive stimulation through temporo-parietal electrodes as a "countershock" following convulsive treatment with frontal electrodes. By this means he claimed to relieve post-convulsive anxiety. (He also found that the "countershock" may enhance depression, which led him to postulate a reciprocal relationship between depression and anxiety.) Following the initial report of Hirschfeld, L. Alexander (1950) studied the effects of subconvulsive stimulation alone, under pentothal anaesthesia, and he concluded that the outstanding effect was reduction of anxiety, "regardless of the diagnostic category of the patient's illness". Subsequently, however, after working with the autonomic test of Funkenstein *et al.* (1949, 1952), Alexander (1953) restricted the indication for electrostimulation to those patients who have epinephrine-precipitable anxiety, i.e. those in whom a minute intravenous injection of adrenaline precipitates an anxiety attack with symptoms which the patient recognizes as a reproduction of his syndrome.

Good results with electrostimulation in anxiety states have also been reported by Wilcox (1951), Yanof (1952), Paterson and Conachy (1952), Berliner and Schartenberg (1952), and with a somewhat different technique by Berkwitz (1952). The majority of these workers believe that abreactions resulting from the stimulation are prognostically favourable and should be exploited

(Hirschfeld, 1949, 1950, 1953; Wilcox, 1951, 1953; Berkwitz, 1952; Paterson and Conachy, 1952). However, Berliner and Schartenberg (1952) maintain that they are merely hysterical phenomena which can be prevented entirely by certain simple precautions. L. Alexander (1950, 1953) does not consider that abreactions are necessary for success. He regards electrostimulation not as part of a psychotherapeutic procedure but as a specific physical method of treatment which should be used in conjunction with psychotherapy. This attitude also governed the management of the present series. The only adverse report to date has been that of Hargrove *et al.* (1953), who obtained better results in the treatment of anxiety states by psychotherapy alone than by a combination of psychotherapy and electrostimulation. They concluded that the addition of electrostimulation to the psychotherapeutic regime introduced problems which might even retard recovery. Unfortunately, their method of control did not ensure that the evaluation was unbiassed, since the investigators were aware of the groupings of their patients.

This information may have influenced their psychotherapy as well as their assessment of the results. The only other attempt at a controlled study has been made by Berliner and Schartenberg (1952), who used each patient as his own control by giving a preliminary course of placebo treatments. Their procedure is open to the objection that the control experiments were effected "during the usual period of extensive pretreatment evaluation of the patient". Moreover, they published no details of their results.

It is generally accepted that almost any electrical wave-form may be used for subconvulsive therapy. Hirschfeld (1949, 1950) originally employed the Reiter current, but he later substituted the Brief Stimulus technique with comparable results (Hirschfeld and Bell, 1951; Hirschfeld, 1953). The majority have employed the Reiter current (Alexander, 1950, 1953; Wilcox, 1951; Yanof, 1952; Paterson and Conachy, 1952; Hargrove *et al.*, 1953), but Berliner and Schartenberg (1952) used Brief Stimuli, and Berkwitz (1952) a faradic current, while Paterson and Conachy (1952) have also used A.C. In the present investigation a modification of the Brief Stimulus technique was employed.

## Apparatus

The stimulator which was used has been described in detail elsewhere (Montagu, 1955). The current consisted of brief, unidirectional, "square waves", the frequency of which could be varied up to 500 pulses per second. The pulse/interval ratio was fixed, so that any change in repetition rate was accompanied by an inversely proportional change in both pulse duration and interval. In consequence, the average current remained constant, for any given peak current, regardless of the frequency of stimulation. The ratio of the peak current to the average current was 20 : 1, and the maximum peak current obtainable was about 100 mA, with good electrode contacts, corresponding to an average output of 5 mA.

Previous experiments with this apparatus showed that a rise in the frequency of cerebral stimulation from 200 p.p.s. to 500 p.p.s. resulted in a progressive increase in the circulating adrenaline (Montagu, 1955). On the other hand, the motor, sensory, and respiratory effects decreased progressively with increasing frequency. These effects were attributed to a greater sensitivity of the sympathetic centres, and a lesser sensitivity of the other structures, to the higher repetition rates and shorter pulses. Two frequencies were therefore used in the present investigation in order to determine whether there was any therapeutic difference at the opposite ends of the scale. The respective conditions were:

| Frequency p.p.s. | Pulse Duration µsec. |
|---|---|
| 200 | 200 |
| 500 | 80 |

The electrodes were circular discs, 3 cm. in diameter, which were covered with a layer of chamois leather soaked in saline. In addition, electrode jelly was rubbed into the scalp at the elected sites.

## MATERIAL

The subjects of this investigation were 100 patients suffering from anxiety states who had been admitted to Roffey Park Rehabilitation Centre. Seventy-five were males and 25 females, with ages ranging from 17 to 58 years. The duration of illness varied from 2 months to 30 years.

The first 50 patients were divided into two equal groups, one of which was treated by stimulation at 500 p.p.s., the other acting as control. These groups will be referred to subsequently as T–500 and C–500 respectively. Two more equal groups were formed from the subsequent 50 cases, one receiving stimulation at 200 p.p.s., the other, again, as a control. These will be known as T–200 and C–200 respectively.

It is impossible to balance groups accurately with respect to the many variants which may influence the course of a neurosis, and it is therefore necessary to select one or two of the more important factors. In the present instance, it was decided to match each pair of groups on the basis of the type of anxiety state, since it was considered that this might be of great prognostic significance. To this end, the patients were subdivided into four types according to the predominant components of their neuroses:

Type 1—Free-floating anxiety.

Type 2—"Conditioned" anxiety, i.e. episodic panic and phobic states occurring in relation to specific situations.

Type 3—Somatic dysfunction.

Type 4—"Displaced" phobic anxiety, e.g. fear of death, doom, or disease.

However, the numbers that could properly be assigned to Type 4 were so small that these were eventually amalgamated with Type 1, so that three categories remained as a basis for matching and for comparison.

No attempt was made to match the groups with respect to age, sex, or duration of illness, since the numbers were fairly large and it was hoped that chance would determine an even distribution. The extent to which this hope was realized is shown in the Table, which demonstrates a greater number of females among the controls. With regard to duration of illness, T–200 constituted a somewhat more chronic population than C–200, but the first pair of groups

TABLE

*Composition of the Experimental Groups*

| Group | Type | | | Sex | | Age | | Duration of Illness | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | M | F | Range | Mean | Less than 10 Months | 10 Months to 3½ Years | More than 3½ Years |
| T–500 .. | 7 | 7 | 11 | 20 | 5 | 24–56 | 32·6 | 6 | 9 | 10 |
| C–500 .. | 7 | 7 | 11 | 16 | 9 | 17–53 | 34·5 | 6 | 9 | 10 |
| T–200 .. | 13 | 3 | 9 | 21 | 4 | 20–58 | 38·5 | 2 | 11 | 12 |
| C–200 .. | 13 | 3 | 9 | 18 | 7 | 17–58 | 35·4 | 4 | 14 | 7 |

was fortuitously matched within the limits of the subdivisions. These were chosen so that in no instance did the duration of illness coincide with a dividing line.

## METHODS

One of the investigators (J.D.M.) acted as a "blind" assessor who was unaware of the groupings of the patients. The other investigator was responsible for all the treatments. The psychometric tests were performed by Mr. V. W. Wilson, Psychologist to the Centre.

Patients who were considered suitable for the series were first referred by their physicians to the assessor. Those who were accepted were placed in their appropriate Types (1, 2 or 3) according to the nature of their neuroses, as defined in the preceding section. The series was then managed as follows:

### (1) *Groups*

The names of the patients and their Type numbers were given to an independent observer, who divided them into the Treatment and Control groups. Further to avoid prejudice, this division was effected on the basis of alternate selection within each Type, i.e. every alternate Type 1 was allocated to the Treatment group and the same with Types 2 and 3. If, for any reason such as physical illness, a patient dropped out of the series, his place was taken by the next entrant of the same Type.

### (2) *Electrical Treatments*

Electrostimulation was performed under pentothal anaesthesia. The dose of barbiturate was adjusted to permit stimulation for five minutes, and with few exceptions 0·5 gm. sufficed. The electrodes were applied bi-temporally about one inch above each ear, and the current was then raised to 4 mA. (80 mA. peaks). This caused initial apnoea (more marked at the lower frequency of stimulation), which usually terminated spontaneously after a few seconds. The current was then maintained at this level for five minutes. In a few cases, a slight reduction in intensity was necessary to promote adequate respiration. Other effects of this current at both high and low frequencies of stimulation have been described elsewhere (Montagu, 1955).

During the first half of the investigation treatments were given on alternate days. This, however, resulted in a reduced rate of discharges, and the programme was subsequently intensified by the institution of daily treatments for five days a week. Twelve treatments were regarded as a standard course but slight variations were not uncommon. At the end of this period the assessor reviewed the cases and referred back to the therapist any patient who, in his opinion, was still improving and might benefit from further treatment.

A total of 631 electrical treatments was given to the 50 patients in the Treatment groups, the distribution being as follows:

| Group | Total | Range | Average | |
|---|---|---|---|---|
| T–500 | 335 | 11–18 | 13·4 | 12·6 |
| T–200 | 296 | 10–12 | 11·8 | |

### (3) *Control Procedure*

There was no manifest discrimination between the Treatment and the Control groups. All the patients congregated at the same time and place and were called into the Treatment room in random order. To the patients' eyes the subsequent procedure was the same in every case: the scalp was cleaned, electrode jelly was applied, and an intravenous injection was followed by oblivion. The controls, however, received on an average only 0·25 gm. of pentothal, sufficient to produce anaesthesia for five to ten minutes in the absence of the electric current. Although the staff was adjured to secrecy concerning the nature of the "treatments", it was feared that a nurse might accidentally enlighten any patient whose curiosity became aroused. To minimize the seriousness of such a slip, a further precaution was taken. Sterile distilled water was dispensed under an imaginary trade name, and 0·5 ml. of this was given to each control by subcutaneous injection after the induction of anaesthesia. The nursing staff was told that the object of the investigation was to compare electrostimulation with the new drug, which was purported to give similar results. In theory, therefore, every patient was receiving some treatment. This security measure appears, in retrospect, to have been unnecessary since, as far as is known, the patients never became aware of the existence of different groups. To the very end, subjects who were, in fact, controls periodically attributed their improvement to the electrical treatments.

A total of 622 "treatments" was given to the 50 controls, the distribution being as follows:

| Group | Total | Range | Average | |
|---|---|---|---|---|
| C–500 | 312 | 10–16 | 12·5 | 12·4 |
| C–200 | 310 | 12–16 | 12·4 | |

(4) *Clinical Assessments*

Each patient was assessed three times: before and after treatment, and finally after an interval of not less than three months following discharge from hospital. A 4-point scale was used, the grades denoting: symptomless (0), mild (1), moderate (2), and severe neurosis (3).

(a) *Initial*—At the first interview a psychiatric history was taken. Particular attention was then paid to two aspects of the case which were regarded as the principal basis for subsequent intra-individual comparison:

i. Symptomatology. An appraisal was made of the subject's particular symptoms with emphasis on the duration, frequency, and severity of each. In addition, the patient was scored on a standard list of fourteen general symptoms and signs, such as impaired concentration, fatigue, disturbance of sleep rhythm, tremor, etc.

ii. Disability. The details were noted under three headings, relating to work, social adaptation, and home life respectively.

No attempt was made to draw inter-individual comparisons. In every case the patient's condition had been deemed sufficiently severe to warrant admission to hospital, and this fact alone was considered adequate justification for adopting a universal score of 3 at the initial assessment.

(b) *Intermediate*—Each case was reviewed within a week after the end of treatment. At this stage it was generally impossible, by virtue of the individual's removal from the work and home situations, to judge any change in disability. The assessment was therefore based almost entirely on symptoms and attitude of mind. Those who were completely or virtually symptomless and were "rearing to go" scored 0, while others who had come to terms with their symptoms were allotted a 1. Grade 2 implied that the patient was still worried about himself and lacked confidence in his ability to return to his premorbid level of adaptation; 3 denoted no improvement whatever.

(c) *Final*—The follow-up was conducted by questionnaire after an interval of not less than three months following the patient's discharge. At this point the residual disability is both more significant and more objective than the symptomatology as a basis for assessment. Particular attention was therefore paid to the subject's adaptation to the work, social, and home situations, and also to the nature of any treatment received in the interim. The questions were designed to be as factual as possible, and all replies were taken into account in reaching a final score. Regrettably, the groupings had by this time been made known to the assessor owing to the necessity for preparing a preliminary report. The scoring cannot therefore be claimed to be free from prejudice. However, in the last section of the questionnaire the patients were asked to assess themselves as either recovered, much improved, moderately improved, unchanged, or worse, and their replies provided a convenient check.

### (5) *Psychometric Tests*

The patients were tested both before and after the treatment period by Mr. V. W. Wilson, who was unaware of their groupings. Two tests were used:

(*a*) Foulds' modification of the Porteus Maze technique (Foulds, 1951). The results of each test were reported as six figures, which denoted the starting time, the tracing time, and the numbers of lifted pencils, wrong directions, crossed lines, and wavy lines respectively.

(*b*) A Word Connection List (Crown, 1952) consisting of fifty stimulus words each of which is associated with a "normal" response word and an "abnormal" response word. The scores denoted the number of "abnormal" responses chosen by the subject.

### (6) *Funkenstein's Test*

This test was performed on each individual before the course of treatment in view of Alexander's claim that only those cases who have adrenaline-precipitable anxiety benefit from electrostimulation (Alexander, 1953). The test was repeated again after treatment in order to determine the extent of the correlation between test result and clinical state which has been reported by Funkenstein *et al.* (1951). Only the first half of the test (reaction to adrenaline) was necessary for these purposes, but the second part (reaction to Amechol) was also, in fact, included on every occasion. The method employed was essentially that of Funkenstein *et al.* (1952) with the principal exception that both parts were performed consecutively on the same day. The test was commenced not less than two hours after the previous meal, and the subject was resting completely for half an hour beforehand. No sedation or other medication was permitted during the preceding 24 hours. The subsequent procedure was as follows:

(i) The systolic blood pressure was repeatedly taken until several consecutive readings indicated that a steady resting level had been reached.

(ii) 0·05 mg. of adrenaline (racemic) in 1 ml. of water was injected intravenously, and the systolic blood pressure was followed at intervals of half a minute until it returned to the initial level. Any manifestations of anxiety were noted, and the patient was questioned concerning subjective sensations. A positive reaction was deemed to have occurred if the injection precipitated either a manifest anxiety attack or symptoms which the patient recognized as a reproduction of his syndrome.

(iii) 10 mgm. of Amechol in 1 ml. of water was injected intramuscularly, and the systolic blood pressure was taken at one minute intervals either until it returned to the pre-injection level or for a maximum of 25 minutes. The patient was again observed and was asked to describe his sensations.

### (7) *Psychotherapy*

Each patient received psychotherapy, coupled with occupational therapy, resocialization, and the other ancillary therapies provided by the Centre. The psychotherapy was given by the subject's own physician but not in immediate conjunction with the treatments, so that no attempt was made to foster abreactions for this purpose. On the other hand, drug abreactive techniques were used as aids to exploration, if indicated. The advantages derived from this system were two-fold. The Treatment and Control groups were alike in receiving the benefit of abreactive measures according to individual need. Secondly, and of great importance, it enabled the psychiatrists to be kept in ignorance of the groupings of their patients.

## CLINICAL RESULTS

The progress of each patient was indicated, on a 4-point scale, by three scores, which denoted the clinical state before, immediately after, and again three months after the treatment respectively (*vide supra*). Subtraction of the intermediate and final scores from the initial score yielded two more figures, both also on a 4-point scale, the degrees of which signified: no improvement (0), moderate improvement (1), marked improvement (2), and complete recovery (3). These scores represented the immediate and the follow-up results respectively.

From inspection of these results it appeared that there was nothing to be gained by retaining the 4-point scale of progress. When the grades were combined in pairs to form only two principal categories of response, as shown below, the patients were found to be divided fairly evenly between them and the results were reduced to manageable proportions:

| | |
|---|---|
| Unimproved | No improvement (0)<br>Moderate improvement (1) |
| Improved | Marked improvement (2)<br>Complete recovery (3) |

The clinical results, both immediate and follow-up, will be considered in terms of this broad division.

### (1) *Immediate Results*

Forty-three of the 100 patients were considered to be improved immediately after the treatment period. When the results were subdivided according to the groupings of the patients, it was found that there was a negligible difference between the Treatment and the Control groups:

| | Unimproved | Improved |
|---|---|---|
| T–500 .. .. | 13 | 12 |
| C–500 .. .. | 12 | 13 |
| T–200 .. .. | 15 | 10 |
| C–200 .. .. | 17 | 8 |
| T–Total .. .. | 28 | 22 (44%) |
| C–Total .. .. | 29 | 21 (42%) |

There was, in fact, a considerably greater difference between the combined "500" groups (50 per cent. improved) and the combined "200" groups (36 per cent. improved) than there was between the totalled Treatment and Control groups. This diminished incidence of therapeutic successes during the second half of the investigation was not statistically significant ($\chi^2=2\cdot0$; $P>0\cdot05$), but it does raise a point of methodological importance, to which reference will be made during the terminal discussion.

### (2) *Follow-up Results*

Replies to the follow-up questionnaire were received from 97 of the 100 patients: 42 of them considered themselves to be either recovered or much improved, and these were classed together as "improved"; the remaining 55 stated that they were only moderately improved, the same or worse, and they were regarded as "unimproved". When these categories were analysed in terms of the experimental groups, it was found that the latter were again well matched:

*Patients' Assessments*

| | Unimproved | Improved |
|---|---|---|
| T–500 .. .. | 12 | 13 (52%) |
| C–500 .. .. | 14 | 11 (44%) |
| T–200 .. .. | 16 | 9 (36%) |
| C–200 .. .. | 13 | 9 (41%) |
| T–Total .. .. | 28 | 22 (44%) |
| C–Total .. .. | 27 | 20 (43%) |

In a few of these cases, however, there was an obvious discrepancy between the patient's remarks concerning the residual disability and symptoms, on the one hand, and the final self-assessment, on the other. In a few more cases, correspondence with the patient was necessary to obtain further information. Ultimately, the assessor's score differed from the patient's choice of category in 15 cases: 10 patients were considered to be unduly optimistic and were downgraded by the assessor, while in 5 instances the reverse was the case. When these alterations were effected, the results appeared as follows:

*Investigator's Assessments*

| | Unimproved | Improved | |
|---|---|---|---|
| T–500 .. | 12 | 13 (52%) | $\chi^2=4\cdot2$ |
| C–500 .. | 19 | 6 (24%) | $P<0\cdot05$ |
| T–200 .. | 17 | 8 (32%) | $\chi^2<1$ |
| C–200 .. | 12 | 10 (45%) | $P\gg0\cdot05$ |
| T–Total .. | 29 | 21 (42%) | $\chi^2<1$ |
| C–Total .. | 31 | 16 (34%) | $P\gg0\cdot05$ |

It is evident from these figures that neither the patients' nor the investigator's assessments showed any significant difference between the totalled Treatment and Control groups. If there was any difference within the series, it must have occurred in relation to the sub-groups. This appears, in fact, to have happened. According to both patients and assessor, approximately 50 per cent. of Group T–500 were improved at the time of the follow-up. Since this result was the same as the immediate response to the treatment, it is clear that the improvement rate had remained steady, in Group T–500, during the interim period. On the other hand, the corresponding figures for Group C–500 indicate that, according to the assessor, half of the immediate successes in this group subsequently relapsed. When a test of statistical significance is applied to the assessor's follow-up findings in these two groups, the difference is found to be significant at the 5 per cent. level of confidence. It could be deduced from this that stimulation at 500 pulses per second exerted a delayed beneficial effect which prevented the relapses that would otherwise have occurred. That this explanation is unlikely to be correct is evidenced by the fact that the assessor found no such tendency to relapse in the second control group, C–200, in fact rather the reverse. It is interesting that so many members of C–500 should have considered themselves to be improved when their remarks contradicted the fact; C–200, on the other hand, showed a tendency to be pessimistic in their self-assessments. Consequently, when the results in T–500 are compared with those in the totalled Control groups, the significant difference disappears ($\chi^2=2\cdot2$; $P>0\cdot05$).

## PSYCHOMETRIC RESULTS

Ninety-six of the 100 patients performed the psychological tests both before and after the treatment period. The results comprised 1,344 scores, of which each subject furnished seven initially and an equal number on retest. From this material two scales of improvement were derived, one for each of the tests. Each scale was then correlated with the immediate clinical response in order to determine the optimal dividing line between "improved" and "unimproved" scores.

### (1) *Porteus Mazes*

The method of handling the Maze results was devised with the assistance of Dr. Foulds. Foulds' figures (1951) have shown that individuals suffering from anxiety states have higher scores than normal individuals on all six of the test factors. The difference was statistically significant for starting time, tracing time, lifted pencils and wavy lines; it was not significant for crossed lines and wrong directions, but the trend was nevertheless noted in these components also. For the present purpose, therefore, it was considered justifiable to include all the factors, each with the same sign, in order to obtain a simple index of improvement. This was achieved by giving to each patient a unit score for every factor which was improved on retest. Inspection of the figures then showed that better definition and correlation with the immediate clinical results were obtained when a bonus of one point was given to each patient whose total tracing time (starting time plus tracing time) on retest was 85 per cent. or less of his initial time. The maximum score was therefore 7. Under these conditions, optimal correlation with the clinical results was obtained with a cutting line between 4 and 5 on the psychometric scale. Scores of 5, 6 and 7 were therefore regarded as indicative of improvement, and scores of 4 or less as unimproved according to the test. The association of these categories with the simultaneous clinical results was then found to fall just short of significance at the 1 per cent. level of confidence:

| | | Clinical | | |
|---|---|---|---|---|
| | | Improved | Unimproved | |
| Psychometric | Improved .. | 25 | 17 | $\chi^2=6\cdot55$ |
| (Mazes) | Unimproved .. | 18 | 36 | $P<0\cdot02$ |

(2) *Word Connection List*

The number of "abnormal" responses on retest was calculated as a percentage of the initial score in each case. If a retest result of 70 per cent. or less of the initial score was taken as the criterion of improvement, optimal association with the immediate clinical results was obtained and was found to be significant at better than the 1 per cent. level of confidence:

| | | Clinical | | |
|---|---|---|---|---|
| | | Improved | Unimproved | |
| Psychometric | Improved .. | 24 | 15 | $\chi^2=7\cdot45$ |
| (Word Connection) | Unimproved .. | 19 | 38 | $P<0\cdot01$ |

These associations were held to provide objective support for the clinical assessments. To obtain further confirmation, the test results were studied in relation to the experimental groups, as follows:

| | Mazes | | Word Connection | | |
|---|---|---|---|---|---|
| | Improved | Unimproved | Improved | Unimproved | |
| T–500 .. | 11 | 14 | 12 | 13 | $\chi^2=1\cdot3$ |
| C–500 .. | 11 | 11 | 7 | 15 | $P>0\cdot05$ |
| T–200 .. | 10 | 15 | 10 | 15 | |
| C–200 .. | 10 | 14 | 10 | 14 | |

With the exception of the Word Connection results in T–500 and C–500, the Treatment and the Control groups were seen to be almost balanced. In the exceptional quarter, there was some difference in favour of the Treatment group, but this difference was not statistically significant.

Although there was a significant association between the results of either test and the clinical findings, it did not necessarily follow that the two tests were in agreement with each other. When their mutual relationship was determined, it was found that there was, in fact, no association between them:

| | | Word Connection | | |
|---|---|---|---|---|
| | | Improved | Unimproved | |
| Mazes | Improved .. | 20 | 22 | $\chi^2=1\cdot5$; $P>0\cdot05$ |
| | Unimproved .. | 19 | 35 | |

This discovery was rather surprising, particularly since both tests yielded identical results in the second Treatment and Control groups. The conclusion that the tests measured different qualities which were not directly related appears to offer the most likely explanation for the discrepancy.

The lack of correlation between the psychometric tests raised the interesting possibility that one may have had greater prognostic significance than the other. However, the dividing lines between "improved" and "unimproved" scores were derived by comparison with the immediate clinical results, so that, to test this hypothesis, it would be necessary to re-determine the cutting scores on the basis of correlation with the follow-up results. This procedure would be unlikely to yield substantially different results unless a large number of the patients had remitted or relapsed during the post-treatment period of observation. A survey of the clinical findings showed that 23 of the 100 patients were considered by the assessor to have changed categories at the time of the follow-up: 9 of these were found to be unimproved immediately following the treatment period but were subsequently classified as improved, while the remaining 14 were considered to have relapsed in the interval. When the corresponding test results were noted, it was observed that the Mazes agreed with 10 of the 23 revised assessments, while the Word Connection List confirmed 14 of them. According to the patients' own assessments, on the other hand, 15 of them remitted in the follow-up interval, while a further 15 relapsed. Only 12 of these 30 changes were supported by the Mazes, and only 15 of them by the Word Connection List. The resulting alterations in balance were considered too small to warrant further attention.

## FUNKENSTEIN TEST RESULTS

Ninety-two of the 100 patients were subjected to Funkenstein's Test both before and after the treatment period. The two parts of the test will be considered separately.

### A. REACTION TO ADRENALINE

The first 25 cases were investigated fully, on the basis of both blood pressure response and subjective effects, as previously described. However, no consistent trend could be found in the measurements, nor did there appear to be any relationship between the blood pressure responses, on the one hand, and the psychological effects of the adrenaline or the clinical state of the patient, on the other hand. In subsequent cases, therefore, the test routine was simplified by omission of the blood pressure readings following this injection. The sole criterion of a positive reaction was considered to be the precipitation of a manifest anxiety attack or of symptoms which the patient recognized as a reproduction of his syndrome.

#### *Correlation with Clinical State*

The results may be divided into four categories according to whether a positive response was obtained initially, on retest, on neither occasion, or on both. The number of times each of these sequences was encountered is shown in the following table, in which the groups are further subdivided according to the immediate clinical response of the subjects:

| Test Result | | Clinical | | |
|---|---|---|---|---|
| 1st | 2nd | Improved | Unimproved | |
| + | — | 16 | 8 | $\chi^2=10{\cdot}98$ |
| + | + | 4 | 18 | $P<0{\cdot}001$ |
| — | — | 21 | 22 | |
| — | + | 1 | 2 | |

It is seen that exactly half of the patients gave a positive response to the first test. Of these, 20 were found to be clinically improved immediately after the treatment period, and in 16 (80 per cent.) of the latter this was accompanied by a negative response to adrenaline on retest. The remaining 26 of the initially-positive cases remained unimproved, and in 18 (69 per cent.) of these the test result remained positive after the treatment period. It is evident that, in those patients who had adrenaline-precipitable anxiety, there was a positive association between clinical state and test result, which was significant below the 0·1 per cent. level of confidence ($\chi^2=10\cdot98$). This conclusion is in accord with the work of Funkenstein *et al.* (1951).

A negative initial reaction is obviously of no significance in this respect, since the reaction would be expected to remain negative in such cases. In fact, according to the results, three patients developed adrenaline-precipitable anxiety during the treatment period, and one of them was subsequently judged to be improved, but these discrepancies are most likely to be due to wrong interpretation of the precipitated manifestations. If, however, the retest results are considered alone, it is seen that positive reactions were obtained in 25 patients, of whom only 5 were found to be improved.

### *Prognostic Value*

To determine whether the reaction to adrenaline was of any prognostic significance, the results of the first test were studied in relation to the clinical results, both immediate and follow-up, as tabulated below. In the follow-up analysis, two sets of figures are given, of which those in parentheses relate to the patients' own assessments of their progress. Only 89 patients feature in these sections, since 3 of the tested subjects failed to reply to the questionnaire:

| First Test | Immediate | | Follow-up | |
|---|---|---|---|---|
| | Improved | Unimproved | Improved | Unimproved |
| Positive .. | 20 | 26 | 14 (17) | 30 (27) |
| Negative .. | 22 | 24 | 19 (22) | 26 (23) |

Statistical tests are unnecessary in order to determine, from these figures, that there was no significant relationship between autonomic test result and clinical outcome. The patients who had adrenaline-precipitable anxiety stood a similar chance of recovering as those who did not.

### B. Reaction to Amechol

The subjective effects of the Amechol were not, unfortunately, noted with any consistency until late in the progress of the investigation. The few observations which were recorded are insufficient to allow any conclusions, and the results have therefore been interpreted entirely on the basis of the blood pressure response. This was regarded as abnormal if there was a fall of more than 10 mm. of mercury which persisted for more than 25 minutes.

According to these criteria, only 10 of the 184 results were abnormal, of which 6 were only just outside the borderline. Three patients gave abnormal responses both before and after the treatment period; two of these patients were clinically unimproved, but the third was found to be improved at the time of the retest. Abnormal responses to the first test alone were encountered in two more cases, one of whom subsequently remitted. A further two patients gave abnormal results only on retest, and both of these remained unimproved.

These numbers are far too small to permit any conclusions, except by virtue of their very paucity. In the light of the work of Funkenstein *et al.* (1949b, 1952), this is an indication that few of the experimental population would have shown a good response to E.C.T. Secondly, with the exception of one abnormal retest response, the results furnish no evidence that the electrostimulation tended to enhance depressive features, and hence the reaction to Amechol, as Alexander (1950, 1953) has reported. The second abnormal response on retest occurred in a control subject.

## DISCUSSION

The 50 patients who were treated by electrostimulation showed no significant difference in clinical response from the 50 controls, during the period of observation. Two psychometric tests confirmed the clinical assessments, which also correlated with the reaction to adrenaline (Funkenstein's test) in those patients who had adrenaline-precipitable anxiety. The immediate results, at any rate, cannot have been influenced by prejudice, since the assessor, the psychologist, and the patients' own physicians were none of them aware of the groupings of the patients.

When the sub-groups were taken into account, an exception to this generalization became apparent: the 25 patients who were treated by stimulation at the higher frequency (500 p.p.s.) maintained their improvement rate in the post-treatment period, while the corresponding control group showed a tendency to relapse. However, this difference, which was significant at the 5 per cent. level, was only observed in the assessor's interpretation of the follow-up reports, and it disappeared when the patients chose their own progress categories. Furthermore, the difference was considered to be an artefact because the second control group showed no similar tendency to relapse, in fact rather the reverse. In explanation, therefore, it may have been due to random sampling; but it is also of interest to remember that this was the only point in the investigation at which the assessor was aware of the groupings of the patients.

The discrepancy, in 15 cases, between the patient's choice of progress category, on the one hand, and the assessor's interpretation of the patient's remarks, on the other hand, has a possible explanation apart from prejudice on the part of the assessor. The patient may have been readmitted to hospital, for further treatment, during the period of observation. In this event, the patient was automatically classed as a treatment failure, regardless of subsequent progress. However, this simple explanation is demonstrably unable to account for the conflicting assessments, since a verdict of "unimproved" was returned by each of the 10 subjects who had received further in-patient treatment, including 4 who had undergone leucotomy.

One unexpected discrepancy emerged from the psychological data: there was no agreement between the two psychometric tests, despite the fact that each supported the clinical findings to a similar high degree. The logical conclusion that each test measured different traits which were not themselves directly related appears to offer the most satisfactory explanation for this anomaly. It suggests an interesting field for further studies.

Several investigators have used electrostimulation as an abreactive measure and have claimed that the emotional outbursts are prognostically favourable (Hirschfeld, 1949, 1950, 1953; Wilcox, 1951, 1953; Berkwitz, 1952; Paterson and Conachy, 1952). However, a recent annotation (Anon, 1952) has emphasized that there is no reason to believe that electrical stimuli will prove superior, in this respect, to any of the pharmacological methods. In the present trial, electrostimulation was investigated as a purely physical method of treatment, which was used in conjunction with—but independently of—psychotherapy. No attempt was made to foster abreactions during the treatments. On the other hand, drug abreactive techniques were used as aids to exploration in both Treatment and Control groups, if required. In view of the absence of concern with electro-stimulated abreactions, it is interesting to note that these rarely occurred. This observation confirms that of Berliner and Schartenberg (1952), who took deliberate steps to discourage such abreactions. They concluded that these outbursts were hysterical elaborations which were motivated by the patient's desire to please and to conform with expectations.

Two possible criticisms of the present trial deserve anticipation. It may be argued that the results were due to the fact that the Controls received better psychotherapy than the Treatment group. This could not have been due to bias on the part of the psychotherapists, since the latter were unaware of the groupings of their patients, but it could still have been caused by accidental mis-matching of the groups with respect to the different physicians. That this was not, in fact, the case is shown by the following figures, which indicate that a good balance was achieved, by chance, in the allocation of the patients:

| Physician | Number of Patients | | |
|---|---|---|---|
| | Treatment | Control | |
| A | 5 | 0 | $\chi^2 = 5 \cdot 70$<br>$P > 0 \cdot 05$ |
| B | 9 | 8 | |
| C | 17 | 19 | |
| D | 13 | 17 | |
| E | 6 | 6 | |

The results may also be criticized on the grounds that the electric current which was used differed from those that have been employed by other workers. While the authors would agree that this criticism is applicable to the higher frequency of stimulation which was given to the first Treatment group, it is scarcely valid in the case of the second group, who were, for that very reason, treated at the lower frequency of 200 pulses per second. The electrical characteristics in the latter case were similar to those which were used by Hirschfeld and Bell (1951), Berliner and Schartenberg (1952), and Hirschfeld (1953), all of whom claimed good results. Furthermore, the central effects of the current, such as the characteristic tonic contractions, were observed to be the same as those which were reported by these workers, as well as by many others who used different types of current.

One final point, of methodological importance, deserves attention. It has been seen that there was a diminished improvement rate in the last 50 cases of the series, and that this was independent of the groupings of the patients. The difference fell short of significance at the 5 per cent. level of confidence, but two probable contributory causes of the trend are nevertheless evident. In the first half of the investigation, the patients were treated three times a week, which led to a reduced rate of discharges from the Centre and an increase in the waiting list. This state of affairs was remedied in the second half of the investigation by the institution of daily treatments. In consequence, the average course of 12 treatments lasted for only a little over a fortnight instead of for nearly a month. Since the cases were reviewed immediately after the treatment period, the last 50 patients had by then had less time to benefit from their hospitalization. In the second place, it is reasonable to expect that the increased waiting list was reflected, to some extent, in the type of case admitted. In fact, as the Table shows, there was a smaller number of really acute cases, and a higher average age, among the last 50 cases of the series. These factors are considered to be important in the following respect: they emphasize again the necessity, in any controlled investigation, for drawing both experimental subjects and controls from the same, contemporary, population.

## SUMMARY

Fifty patients who were suffering from anxiety states were treated by subconvulsive electrostimulation through bi-temporal electrodes under pentothal anaesthesia. In the first 25 of these cases, the frequency of stimulation was 500 pulses per second; the remaining 25 were treated by stimulation at the lower frequency of 200 p.p.s.

Fifty similar cases, likewise divided into two equal groups, acted as controls. They received a course of placebo "treatments", which also included pentothal anaesthesia. No other discrimination was exercised between the Treatment and the Control groups.

Each Treatment group was matched with the corresponding Control group on the basis of the type of anxiety state, according to a simple classification. To prevent prejudice, the classified patients were divided into the Treatment and Control groups by an independent observer and on the basis of alternate selection within each Type.

The average course consisted of 12 treatments or of the same number of control "treatments". In addition, each patient received psychotherapy from his own physician. No attempt was made to foster electrostimulated abreactions for psychotherapeutic purposes.

Two psychometric tests were performed on each patient both before and after the treatment period. The patients were also subjected to Funkenstein's test of autonomic reactivity on both occasions. A follow-up was conducted by questionnaire after an interval of not less than three months following the patient's discharge.

The assessor, the psychologist, and the patients' own physicians were all unaware of the groupings of the patients. Unfortunately, however, these had to be made known to the assessor before the follow-up reports were interpreted. Each patient was therefore asked, in addition, to make a self-assessment, which was used as a check.

The results indicated that:

(1) There was no significant difference in clinical response between the 50 treated cases and the 50 controls, during the period of observation.

(2) At one point there was a significant difference between one Treatment group and the corresponding Control group. However, this difference, which was in favour of the Treatment group, was only observed in the assessor's interpretation of the follow-up reports, and there were reasons for believing that it was unrelated to the treatment.

(3) There was a significant association between each psychometric test and the immediate clinical findings. Furthermore, neither test revealed any difference between the sub-groups. Surprisingly, however, no agreement was found between the two tests, and it was concluded that they probably measured different traits.

(4) The reaction to adrenaline, in Funkenstein's test, was associated very significantly with the clinical findings in those patients who had adrenaline-precipitable anxiety.

(5) The reaction to adrenaline was of no prognostic significance. Patients who had adrenaline-precipitable anxiety stood a similar chance of improving as those who did not.

(6) The reaction to Amechol provided no evidence that electrostimulation enhanced depressive features.

(7) Regardless of their groupings, nearly half of the patients were found to be much improved immediately after the treatment period, and more than a third of them maintained their improvement for at least three months. While these results leave much to be desired, any new form of treatment must be able to better them substantially before it can be considered to be of any therapeutic value.

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# PROLONGED SLEEP TREATMENT IN MENTAL DISORDERS (SOME NEW PSYCHOPHARMACOLOGICAL CONSIDERATIONS)

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SLEEP as a method of controlling mental derangements dates to antiquity. According to Celsus sleep restores mental equilibrium: "but certainly for all so affected sleep is both difficult and especially necessary; for under it many get well . . ." (13). Griesinger in 1861 was the first to use chloroform as a sleep-inducing agent in mania and melancholia (21). The advent of bromides and barbiturates enhanced further investigation, and early in this century sleep treatment was relatively well systematized by Wolf in 1901 (40), Trenel in 1903 (39), and by Kläsi in 1922 (25). This paper will not attempt to review the literature on sleep, for these findings have been outlined in papers by Palmer (32, 33), Baer (7), Ey (18), and recently in a documented book by Angel (2). The purpose of this paper is to present (1) a method of prolonged sleep treatment using the new inhibitory substance chlorpromazine (Largactil), in combination with different barbiturates in an attempt to provoke a sleep pattern as similar as possible to normal sleep, in contrast to deep unconsciousness advocated previously (14, 32); (2) to discuss underlying theories of sleep treatment, and propose some new formulations; (3) to suggest future use and investigation of the treatment; and (4) to bring to the attention of American psychiatrists a treatment which holds an eminent position in Europe, particularly in the U.S.S.R. where sleep therapy appears to be the only officially accepted form of treatment in mental illnesses.

## MATERIAL AND METHOD

This paper is based upon a study of 25 cases, followed for 12 months or more. Five of these have had a 24-month follow-up. These 25 cases had not responded to any other form of treatment, ranging from electric shock to long-term psychotherapy, and in each case the sleep treatment was used as the last resort. Classified diagnostically there were: 8 schizophrenics, 2 manic depressives, 3 obsessive compulsives, 9 mixed psychoneuroses, 2 hysteria and 1 character neurosis.

The age range was from 19 to 44, with an average age of 30. Prior to treatment all cases received a routine physical examination, and EEG, and a psychological investigation.† The EEG was repeated four days following the termination of treatment. Four months following treatment, four cases were retested with a psychological battery including: the abbreviated Wechsler Bellevue scale, Figure Drawings, and Rorschach. Since chlorpromazine (Largactil), the medication added to the routine barbiturates, was known to have an hepatoxic effect, three liver function tests were carried out, including cholesterol and serum bilirubin studied once weekly, and alkaline phosphatase studied twice weekly. (Experience with this drug in the past (5, 38) proved that these weekly liver function tests were sufficient warning agents of possible commencing liver damage.)

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The actual sleep method used has been the result of modification of the treatment used in Europe, primarily in Ey's clinic where the author assisted in its administration. The goals were to produce by medication a prolonged sleeping state, approximating as closely as possible the normal physiological state; that the patient was to sleep twenty to twenty-two hours daily; and that he could be treated easily and swiftly by well trained psychiatric nurses. These goals were at least partially realized by the following procedures: (1) combining three different time-reacting barbiturates which would produce a sustained level of sleep, i.e. as one barbiturate was declining another was reaching its maximum effect. Seconal was chosen as a short acting barbiturate, Nembutal as one of moderate reaction time, and barbital or phenobarbital as long acting medications. (2) chlorpromazine (Largactil) was added to the above combination because it seemed it would be a useful contributor to the sleep treatment in view of its regulatory effects on different mental syndromes (5, 27), as well as its barbiturate-potentiating effects. The addition of this drug permitted a reduction in the amount of barbiturates that had to be administered, produced a smoother sleep course, and provided a medication that could be maintained after the sudden cessation of the other barbiturates. In all cases all the medication with the exception of the Largactil was stopped at the end of the sleep treatment. This sudden cessation of medication was based partly upon Heldt's report (22) that the post-delirium state sometimes following prolonged barbiturate narcosis was the main therapeutic aspect of the sleep treatment.

Two nursing methods were used according to the degree of the patient's tolerance, the degree of adaptation, and the smoothness of the sleep: (1) A triple-waking technique: the patient was awakened three times a day, at 8 a.m., 2 p.m., and 8 p.m.; and (2) A double-waking technique: the patient was awakened twice daily, at 8 a.m. and 8 p.m. Experience showed that the first technique was safer, and a less stressful form of treatment. An attempt was made to limit the maximum total nursing care of each period to one hour. During this hour temperature, pulse, blood pressure, and respiration were taken before the patient was moved out of bed to get cleaned, etc. and then he was encouraged to eat anything he liked, sitting on a chair. Solid food would usually be taken in the first week, and from then on semi-solid foods. The minimum amount of calorie intake was 1,500, and the minimum amount of fluid intake was 2,000 c.cm. daily; the latter was modified according to the output. In addition, all patients received extra vitamin B and C parenterally. The nursing care between waking periods consisted of changing the position of the patient every two hours and administration of a mixture of oxygen–carbon dioxide if the respiration became shallow (this was necessary in only two instances). To facilitate the excretory functions patients received milk of magnesia routinely every other day, and were given a colonic irrigation if no elimination had occurred in two days. Catheterization was performed within ten hours if the patient had not urinated spontaneously. Five units of regular insulin were given half an hour prior to each meal in order to increase the appetite.

The basic medical formula was the following:

| | | | |
|---|---|---|---|
| Seconal | gr. 1½ | or | mgm. 100 |
| Nembutal | gr. 1½ | or | mgm. 100 |
| Barbital | gr. 2½ | or | mgm. 150 |
| Phenobarbital | gr. 3 | or | mgm. 200 |
| Chlorpromazine | | | mgm. 50 |

This formula can be adjusted quite easily in the first few days according to the degree of wakefulness. In order to have a more or less standard measurement, the degree of wakefulness was divided into four grades, in relation to stimuli which were utilized systematically in the following order: light (opening of the door, flashing light on the patient); sound (non-verbal, verbal); touch, movement (part, and whole body); and pain. According to the responses to these stimuli the following qualitative four grades were adopted:

4—Patient wakes up, opens his eyes, talks freely, moves in and out of bed relatively unaccompanied, and eats alone.
3—Patient wakes up, opens his eyes, talks with difficulty, moves in and out of bed slowly, and has to be fed and be accompanied.
2—Patient wakes up, opens his eyes, talks with difficulty, can move in bed but not out of bed unaccompanied, and has to be fed.
1—Patient wakes up, opens his eyes, mumbles, and moves in bed.
0—Patient wakes up, does not open his eyes, does not talk, does not move except for a few movements indicating his waking up.

These grades were used by the nurses, and the medication could be adjusted accordingly, even without the physician seeing the patient. Usually doubling the dose of two barbiturates was enough to change the degree of wakefulness about one grade. It was found that in the case of restlessness, particularly at night, one intramuscular injection of hyoscine gr. 1/150 and apomorphine gr. 1/60 was enough to carry the patient over till the next medication. It is important to note that the amount of barbiturates required and the degree of smoothness of the sleep was greatly dependent upon the willingness of the patient to accept the treatment. For this reason, as observed by other authors, all patients were interviewed at length prior to the treatment, the procedure explained, and a motivated consent obtained. In three patients, who in the second week of treatment became restless and resistant to taking medication, it was found that the administration of Seconal gr. 1½ ten minutes prior to the intake of the medication during the meal was sufficient to provoke a sufficient degree of drowsiness and co-operation in order that the other drugs would be taken with little resistance.

## RESULTS

The following Table indicates the overall results in the 25 cases, according to their diagnostic classifications. There was improvement in 15 cases (9 markedly improved and 6 moderately improved).

TABLE I

| Clinical Diagnosis | Number of Cases | Marked Improvement | Moderate Improvement | No Improvement |
|---|---|---|---|---|
| Schizophrenia .. .. | 8 | 3 | 2 | 3 |
| Manic-depressive .. | 2 | 2 | – | – |
| Obsessive-compulsive .. | 3 | – | – | 3 |
| Mixed Psychoneuroses .. | 9 | 3 | 2 | 4 |
| Hysteria .. .. .. | 2 | 1 | 1 | – |
| Character Neurosis .. | 1 | – | 1 | – |
| Total .. .. | 25 | 9 | 6 | 10 |

*Schizophrenias*

Eight chronic remitting schizophrenics, refractory to all other treatments, received an average of twenty-five days of sleep. Three cases showed marked, and two moderate improvement. The improvement consisted of the capacity to organize their social life and appear "normal" to their close relatives. However, it should be noted that in two cases, who showed marked improvement, the Rorschachs performed four months after treatment revealed no particular change in the schizophrenic structure of personality as compared to the pre-sleep Rorschachs, except for the strengthening of some defences.

These results with schizophrenics are in contrast to those of French authors who found few improvements in this particular mental syndrome. However, Ivanov-Smolenski (quoted by Wortis) finds the results comparable to those treated with insulin coma; and, in fact, the cases with preponderance of affective features responded better to sleep, while cases with florid symptomatology were benefited more by insulin.

### *Manic-Depressives*

At the beginning of our experience with sleep we used prolonged sleep in one case of florid maniacal symptomatology, and another mixed case of agitated-depression. Both cases showed marked "clinical cure". But since then Largactil alone (5, 27) has proved sufficient to control the maniacal states, and there has been no need to use prolonged sleep in this affection. However, we were impressed by the repetition of a triple cycle of mood change in the two cases mentioned. While in sleep, the maniacal state changed, in the first week, into a depressive mood, which then, in the second week, changed into a second maniacal episode, and finally the mood returned to "normal" at the termination of treatment. One may try to explain this change by the concept of regression, and the fact that the depressive state may be a deeper state of regression provoked by organic assault combined with evident psychological dependency state initiated by sleep. Later when the unknown reorganizing effects of sleep set in, a progression to the maniacal defence state occurs, followed by a more or less complete reorganization and normalization.

### *Obsessive-Compulsives*

Three cases with longstanding obsessive-compulsive complaints, and marked rituals showed only slight improvement after an average of twenty-five days of sleep. In one case the washing rituals decreased from three hours to one. Like most other treatments in this neurosis, this therapy proved to be of little benefit.

### *Other Neuroses*

Nine cases of chronic mixed psychoneuroses with a variety of complaints (anxiety, hypochondriasis, hysterical reactions, obsessive-compulsive trends, etc.) received an average of twenty-five days of sleep. Three patients showed marked improvement and two moderate improvement. The improvement consisted of the ability to reorganize their social life, the disappearance of symptoms, and the return of their behaviour to "normal", as judged by the relatives. Three of the improved cases developed strong feelings and behaviour of dependency. Two of these patients gradually overcame this dependency following routine supportive psychotherapy, and the other worked through this dependency in a non-directive form of psychotherapy.

Two cases suffering from typical hysterical symptomatology underwent thirty days of sleep. One, with dull intelligence, moderately improved and was able to resume her social life. The other showed a complete recovery not only in her symptoms, behaviour and social life, but also in her personality structure, assessed clinically and by the Rorschach. This test taken four months after the treatment and compared with her pre-sleep Rorschach showed marked improvement and stabilization, a release of creative energy, the establishment of better intellectual control, a better control of emotional responsiveness, and a considerable strengthening of the defences. Our results with neurosis confirm those of other writers.

A moderate improvement was noted in a typical case of so-called character neurosis who had not responded to prolonged psychotherapy. This improvement was transitory however, and the patient relapsed, but with lesser intensity, about eight months after treatment.

### *Complications and Changes*

There were some minor complications such as sudden rise of temperature to 103–104° and then a sudden fall to normal within 12 hours in 3 cases; maculo-papular rash in 2 cases, which disappeared completely after the cessation of treatment. Other more important complications were as follows: post-sleep convulsive seizures in 2 cases, one being an epileptic with mixed psychoneuroses; a mild peripheral radial paralysis of the left hand in one case, which disappeared within a month; a Parkinson-like syndrome in two cases, probably due to the effects of Largactil; and one case of bronchopneumonia in the 17th day of sleep which recovered promptly under antibiotics. This case was among our early cases.

Two cases showed slight liver damage manifested in rise of alkaline phosphatase, which declined rapidly after the cessation of Largactil. There was no evidence of brain damage.

The EEG's of 7 patients were examined before and a few days after prolonged sleep therapy. Changes following treatment were quite consistent. Alpha activity, if present, was at a slower frequency than before treatment. Frequently the predominant rhythmic activity was in the theta range at 6–7 c./sec. All records contained considerably more bilateral theta activity than observed prior to treatment. The general effect was one of slowing of brain rhythms.

Photic stimulation was carried out as part of the EEG examination. No patients displayed a photomyoclonic response prior to treatment. After treatment 4 of the 7 gave a photomyoclonic response" (35). This finding would be anticipated from Shagass's (36) observation that the photomyoclonic response is elicited frequently shortly after apparent clinical recovery from barbiturate coma.

All in all, the complications were minimal, and even in one case who was suffering from urinary infection before treatment, the sleep could be started and terminated successfully by the use of an indwelling catheter. This relative lack of complications is in contrast to the experience of some other investigators using other methods (14, 33).

### *Theories of Prolonged Sleep Treatment*

Three types of theories will be discussed as underlying the type of sleep action and its effects on the organism. First we will discuss the various physiological theories, then the diverse psychological concepts, and lastly the organodynamic theory which attempts to combine the former two approaches.

Muller (31) considered the mode of action of sleep thought as a chemical rearrangement of the vegetative nervous system, an opinion later shared by Monnier (30). Hess suggested that sleep has a particular function in preventing the psyche from exhaustion (23). Boss (9) expressed a similar view. He believed that sleep restores energies which maintain the ego in consciousness. Palmer (32) in a similar approach stated that sleep results in a type of psychosomatic rest allowing both somatic and psychological restitution. The problem of central nervous system "rest" is not a new proposition; as we said at the beginning Celsus believed in the restitutive function of the sleep. It seems that the point of view held by Russian authors, which is admittedly a totally physiological hypothesis, has the same basis (10, 41). The Pavlovian conceptions of the roles of the cortex are those of inhibition, excitation, and control. In some instances the cortex is incapable of controlling and inhibiting the impact of stimuli from the diencephalon to the degree that all the arriving signals become exaggerated and cortical responses, even to weak stimuli, become violently progressive. This results in the formation of subcortical chain reactions which alter visceral and central nervous system functioning. The purpose of sleep treatment in this concept is to allow a temporary disconnection of the exhausted cortex, which allows the restitution and reorganization of cortico-subcortical connections. This is explicit in Pavlov's concept of "protective inhibition" provoked by sleep: "a state of depressed or suspended nervous activity which has important restorative and regulative effects on nervous functions" (41). It should be noted that the concepts of inhibition and excitation are totally hypothetical.

The recent opinion of some French authors (16) concerning the effect of Largactil on mental syndromes is similar to the above. Largactil, by its sympathicolytic and inhibitory effect, provokes a modified form of hibernation without refrigeration. This hibernation, in some instances when the fundamental pathology is a hyperactivity of the adaptative processes, puts the organism at rest and results in restoration of functions and improvement.

As far as the psychological theories of sleep go, it is beyond the scope of this paper to discuss this problem fully. What appears relevant to the matter under discussion is the fact that, psychodynamically speaking, in recent years a gradual shift has occurred from the original emphasis Freud put upon the release and satisfaction of drives in sleep to its defensive character. Furrer (20) stressed the possibility of a better ego-organization during sleep after the release of excessive libidinal drives from associative constellations. Simmel (37) noted the function of sleep as a defence against aggression to the therapist. Bird recently has stressed similar views. For him sleep can serve as a defence against aggression "not by shutting out aggressive fantasies but particularly by inhibiting motility" (8). Scott (34) considering the same problem spoke of sleep as a "regressive defence".

It may be that the beneficial effects of sleep therapy are due solely to its psychological significance, and the manner in which the patient consciously and unconsciously utilizes it emotionally. Sleep puts the patient in a complete state of dependency, where all apparent needs are fulfilled. This dependency itself, as was pointed out by Heldt (22), may be the important therapeutic element. Dependency may become the turning point of a pathological sequence of events. In fact, in our improved cases one schizophrenic and three neurotics developed marked dependency on the therapist which was the starting point which allowed further constructive treatment. However, there were no particular personality trends or conflictual settings common to all these patients. Some improved cases did not show dependency. However it should be emphasized that in those who developed dependency, this behaviour could be therapeutically utilized. The important point in our improved cases was that, clinically as well as in psychological tests, there was a change in the defence system, allowing better ability to control and integrate conflicts. In other words, a strengthening of the ego had occurred. In almost all neurotic patients who improved, the important psychological factors prior to sleep were the weakness of defences and the imminence of the release of most of the drives and action tendencies. However, many of the unimproved cases also had similar psychodynamics.

Although evidence indicates the importance of psychologic factors in the aetiology of sleep, in its maintenance, and its cessation, it does not seem to the writer that they can be applied *in toto* and directly to pharmacologically provoked prolonged sleep. In this instance sleep is enforced and it is not the outcome of the conflicting tendencies originating within the organism, although it has considerable effect upon them, and it is subsequently psychologically assimilated and invested by the organism. The explanatory theory should be, in the present situation, psychophysiologically relevant. In sleep disturbances—and most of our patients showed these disturbances—the problem resides within the different psychic instances in full function, while here the sleep is provoked *beyond* and *in spite* of internal conflicts. It appears to the writer that the conceptual framework of sleep should be organo-dynamically* oriented. The same is true for normal daily sleep in which both organic and psychologic factors play a role. In pharmacologically prolonged sleep, however, the organic factors are in the foreground and are the first events in the sequence of "physiological process—total organism—psychological process" (3). In psychologically induced sleep (during psychotherapy, in hypnosis, etc.) the sequence is in reverse, i.e. "psychological process—total organism—physiological process". What follows is a series of inferences and concepts along this line which may render comprehensible some, and only some aspects of prolonged sleep treatment.

The role of the central reticular activating system in the states of wakefulness, arousal, and sleep has been recently emphasized (19, 28) and it appears that they should, logically, form the first series of organic events in the theory of prolonged sleep. It appears that the activity of this system is responsible for what can be called "attentive prehension" of the internal and external events (6). Put otherwise, it can be said that through the diffuse influence of this system the organism is put in a state of effective or active "presence in the world" (6). Kubie (26), and Azima, Cramer and Faure (6) have postulated that some functional neuronal systems are concomitant and underlie some unconscious processes, and may be represented, theoretically, as composed of some self-sustaining, self-repetitive, self-energizing neuronal sets beyond the active phase of other neuronal patterns. It appears logically consistent to maintain that the establishment of a relationship between these self-sustaining systems and the non-specific reticular system puts the organism in a state of attentive and effective prehension of the events represented subliminally before, and provokes what can be designated as emergence of unconscious processes into consciousness. If this hypothesis is plausible some psychotherapeutic events such as more or less sudden insight, abreaction, breakdown of defences, release of drives can become psychophysiologically somewhat comprehensible. It is known that barbiturates inhibit and deactivate the reticular system, and recently the same phenomena have been illustrated with the use of chlorpromazine (24). Thus during the sleep treatment the systems responsible for the support of some conscious processes remain for a long time in a state of low energy, inactivity, or relative refractoriness. It is consistent to continue the inference and say that in this state those self-sustaining and self-energizing systems of unconscious activity can form functional relationships much more easily with the reticular system, because the latter system is deactivated and does not hinder the propagation into it. Hence much of the self-energizing action tendencies can be released and come into relationship; in other words, become integrated with other functional neuronal sets. In our experience marked abreactive phenomena in relation to unconscious life relationship of the patients would emerge in verbal and behavioural form within a week in almost all cases. It was said at the beginning that pharmacologically produced sleep is forced upon the organism beyond and in spite of psychodynamic structure of the personality. If we consider what we said about the relationship of the reticular system to conscious and unconscious systems, and if, in addition, we consider that voluntary effort is necessary for normal sleep, and that the ego interferes in inducing and maintaining the sleep, it follows that in pharmacologically prolonged sleep we are dispensing with the services of the ego and voluntary effort and we are not allowing the organism to utilize the available energy and action tendencies of this aspect of the psyche. We are producing a state of sleep where the ego is more or less not involved, its defences are not used, its substantial structure is inhibited and put at rest for awhile. This relative inactivation of the integrating systems allows and helps explain the emergence and release of repressed action tendencies and drives, with subsequent gratification, exhaustion and reintegration, while the ego system has not lost any of its energetic tendencies. Following sleep, the ego may even appear strengthened, since some underlying conflicts have been abreacted and no longer necessitate the maintenance of some non-contributing defence mechanisms. For example, during sleep the dependency and passive needs are allowed to be released and gratified. In awakening, the passivity may be accepted as such, non-conflictually, and can be psychotherapeutically utilized without a defensive super-structure. This was demonstrated in four cases where the pre-sleep behaviour consisted mainly of destructive aggression evolved chiefly as reaction formation against unacceptable passivity.

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* The term "organo-dynamism" was first used by H. Ey for his general conception of Psychiatry and Neurology (4, 17). The writer takes as theoretically meaningful only the first premise of this conception, from which the above inferences are derived.

There remain many other points and objections to be considered. The above formulation may be useful in an organo-dynamic understanding of some aspects of prolonged sleep treatment.

### *Indications for Sleep Treatment*

As yet there is not a general consensus of opinion about the indications of prolonged sleep therapy. It appears, however, that neuroses and psychosomatic syndromes respond more readily to this treatment. Andreef (1), who has treated more than 350 cases, gives the following indications in order of preference: peptic ulcer, hypertension, visceral neuroses, causalgia, phantom-limb, and refractory ulceration of extremities. Davidenkov (15) in his experience with 118 cases supports this general outline, and so does Ey's recent report (18). It should be noted that Russian authors look at the problem of neuroses and psychosomatic syndromes in a purely physiological manner. They believe that sodium amytal induces a physiological release of psychomotor functions which is very effective in a state such as stupor. They disclaim any complex intrapsychic mechanisms (Wortis). In schizophrenias the reports are equivocal. Ey's results have been very poor, while Clapp and Loomis (14) report a favourable impression with their continuous method of sleep therapy. According to Ivanov-Smolenski (cited by Wortis) prolonged sleep treatment gives similar results to insulin in the treatment of schizophrenias. Our experience, on clinical grounds only, supports this opinion. It is generally agreed that sleep alleviates, at least temporarily, the maniacal or agitated depressive states.

Our experience is too limited to permit a definitive outline, but our tentative list of indications is as follows: neuroses, in particular conversion hysteria, anxiety hysteria, and borderline cases with predominance of hysterical and anxiety symptoms; hypochondriacal and psychosomatic syndromes; schizophrenic reactions with preponderance of affective alterations and excitation. Obsessive-compulsives appear to benefit very little by sleep, while manic-depressive states can be treated with success with Largactil alone.

## COMMENTS

The present form of prolonged sleep treatment, as presented in this paper, has some advantages over some of the previous methods. Chlorpromazine (Largactil) permits a considerable reduction of barbiturates, in addition to its inhibitory effects, and the combination of three time-reacting barbiturates allows a more sustained and near-physiological level of sleep, which in turn reduces the nursing care. It is very probable that by providing a particular section for sleep therapy in the hospital, by providing a uniform setting, and by utilizing some additional procedures, as used by Russian authors, one may induce a pattern of conditioning whereby sleep is provoked with very small amounts of barbiturates.

The question arises as to the value of sleep therapy, for as will be noted the rate of recovery (60 per cent.) is no higher than other forms of treatment. It should be noted, however, that this rate of recovery occurred in intractable patients who had not responded to any other form of treatment. The important point seems to be how to select those cases which will respond to sleep therapy and not to others, and are likely to profit more from this specific type of therapy. It seems necessary to study carefully the personality changes during and following the sleep that will provide criteria for the selection of cases for such a treatment.

Prolonged sleep appears to offer many possibilities both as a primary or adjuvant therapeutic tool. Two future applications which may render a promising service for the therapy of mental disorders are: (1) to provide a setting for anaclitic therapy (29); (2) to provide a setting in which "psychic driving" (11, 12) may be instituted. Both of these applications have been utilized. In one case* this anaclitic therapy was applied with much success. The patient was a severe chronic neurotic young woman who had not responded to any kind of therapy. She was put to sleep, fed and medicated by the therapist who provided an intimate setting of mother–child relationship. A marked regression occurred and the patient actually behaved like a baby. This behaviour was psychotherapeutically utilized during the sleep, which resulted in a post-sleep progression and subsequent improvement. An important point in this case was the externalization of forgotten memories during the sleep, with a post-sleep abreaction and living through of these once repressed conflicts. The latter phenomenon illustrates the reversibility of the amnesias reported after prolonged sleep. In another chronic neurotic a very marked regression occurred during prolonged sleep to the extent that there was a complete re-enactment of infantile patterns of behaviour. Here also there was a spontaneous rapid progression post-sleep with subsequent improvement.

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* We are indebted to Dr. Shirley Ferguson for the treatment of this case.

Sleep therapy may provide a situation, *par excellence*, for what Cameron (11, 12) has termed "psychic driving" and "dynamic implantation". This method employs the play-back technique originated by Cameron by which certain relevant psychodynamic themes are recorded back to the patient using his, or the doctor's voice. This technique as it were, implants and forces the patient to identify the problem of the repeated verbal stimuli. It also allows the individual to separate his underlying drives from his conscious controlling power; in other words, an "ego-distancing" is allowed between his drives and his ego tendencies (between the primary and secondary processes), and initiates a reintegration and a working through of the problems. Attitude changes were noted in the themes of repeated T.A.T. cards of one patient who following the prolonged sleep psychic driving was able to recognize overtly her formerly disguised hostility to her mother. Further investigation of the combination of prolonged sleep and "dynamic implantation" offers new avenues to therapeutic intervention.

## SUMMARY

1. A method of providing a prolonged state of sleep, approximating as much as possible the normal physiological state, is described. This was accomplished by the combination of different time-reacting barbiturates and chlorpromazine (Largactil). The minimum daily sleep time was twenty hours, and the average duration of treatment, twenty-five days.

2. Eight schizophrenics, 2 manic-depressives, 3 obsessive-compulsives, 9 cases of mixed psychoneuroses, 2 hysterics and 1 character neurosis, most of whom had not responded to any other treatment, were treated. They have been followed from 12 to 24 months.

3. Improvement was noted in 60 per cent. of the cases. This improvement was based upon social and behavioural normalization. Four cases had extensive pre- and post-sleep psychological tests.

4. There were very few complications: two transitory maculo-papular rashes; post-sleep convulsive seizures in two cases, one being a recognized epileptic before treatment; one case of pneumonia which responded very rapidly to antibiotics.

5. Indications for prolonged sleep treatment of psychiatric syndromes are discussed and the following tentative list is proposed: neuroses, in particular conversion hysteria, anxiety hysteria, and borderline cases; hypochondriacal and psychosomatic syndromes; schizophrenic reaction with preponderance of affective alterations. Obsessive-compulsives do not respond to sleep, and maniacal cases respond to chlorpromazine alone.

6. Theories of sleep are briefly discussed. A new organo-dynamic formulation is outlined.

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# ALZHEIMER'S DISEASE CONFIRMED BY CEREBRAL BIOPSY: A THERAPEUTIC TRIAL WITH CORTISONE AND A.C.T.H.

By

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THIS paper describes treatment with cortisone and A.C.T.H. of two patients in whom Alzheimer's Disease (A.D.) had been confirmed histologically by cerebral biopsy.

A.D. is a progressive dementia which usually occurs between the ages of 40 and 60 years, and there is no known specific treatment. Intellectual deterioration, which progresses insidiously over a period of 2–10 years, leads to gross dementia, and the inevitable problems of care and supervision often necessitate removal to an institution. Histologically the disease is characterized by atrophy of cortical nerve cells and the presence within the cortex of argentophile plaques which are demonstrable by the silver impregnation techniques of Bielschowsky or von Braunmühl (see Fig. 1); these plaques have a mixed granular and fibrillary structure. The same silver methods also show irregular thickening and disorientation of the nerve cell fibrils, which form "tangles" and "loops" (see Fig. 2). Identical plaques and neurofibrillary changes are also seen in senile dementia, the term "senile plaque" being used in both diseases.

In recent years A.D. has been reviewed by McMenemey (1940 and 1941), Newton (1948), Sjögren *et al.* (1952) and Neumann and Cohn (1953). Further review is outside the scope of this communication, and for detailed clinical and pathological features reference should be made to these papers. We have accepted the postulate of McMenemey (1940) that "All cases, at any age, showing an abundance of senile plaques, neurofibrillary changes and cell atrophy, which cannot be regarded as senile dementia, belong to the Alzheimer category." Stengel (1943) attempted to differentiate the disease on clinical grounds but our experience, in common with that of other authors (Newton, 1948; Sjögren *et al.*, 1952; Green *et al.*, 1952) is that it may be difficult to separate A.D. clinically from other diffuse diseases of the cortex.

Because of the inadequacy of all forms of therapy, it was decided to assess the effects of cortisone and A.C.T.H. in A.D. The use of these drugs in the treatment of incurable diseases of the nervous system has since been described by Glaser and Merritt (1952) with negative results. Their cases included Disseminated Sclerosis, Amyotrophic Lateral Sclerosis, Progressive Muscular Atrophy, etc., but not A.D. Two patients who showed mental deterioration and other features which approximated clinically to those associated with A.D. were selected for therapeutic trial. Before starting treatment, it was essential that the diagnoses were established beyond reasonable doubt, and it was possible to do this only with the help of cerebral biopsy. This procedure was therefore undertaken after carefully weighing the possibilities of a new form of treatment against the hopelessness of doing nothing. Pick's Disease had already been confirmed by cerebral biopsy (Polatin *et al.*, 1948) and since we applied it to A.D., Green *et al.* (1952) and Goodman (1953) have recorded cases of A.D. similarly confirmed. It was realized that a negative biopsy would not necessarily exclude A.D. as the lesions are usually said to be irregularly distributed throughout the brain; slight changes would also fail to establish a firm diagnosis. These are mainly theoretical objections, for in their paper on cerebral biopsy on presenile dementia Green *et al.* (1952) state, "Considering the severity and omnipresence of Alzheimer cells and senile plaques in A.D., it is difficult to imagine that they would be entirely absent in even a small piece of tissue such as a biopsy." Both our patients showed abundant Alzheimer changes which, together with the clinical findings, confirmed that the disease was present.

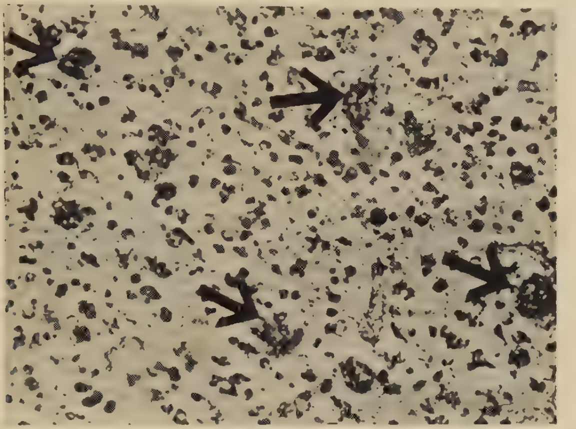

FIG. 1.—Cerebral biopsy showing argentophile plaques in the cortex (von Braunmühl's method).

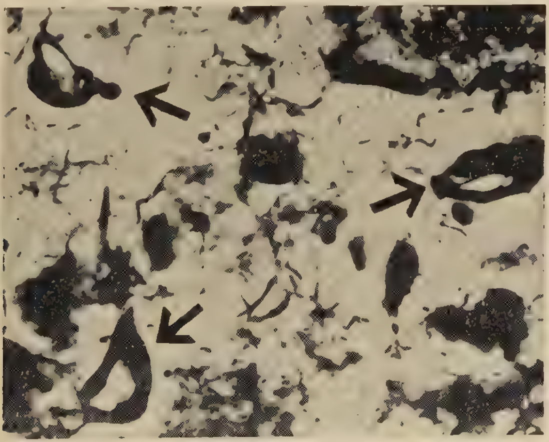

FIG. 2.—Cerebral biopsy showing neurofibrillary changes (von Braunmühl's method).

## CASE REPORTS

*Case 1.* H.C., male, aged 52, was referred to the O.P.D. of the Midland Hospital for Nervous Diseases on 27.12.51 with a history of rapid deterioration both of memory and general efficiency over the past 18 months. Prior to this he had been an energetic person, holding a responsible job for over 20 years, and played an active part in the works' cricket team. His wife now had to do everything for him, including dressing. The first mental symptoms were of a depressive nature and he had elsewhere received a course of E.C.T. without benefit.

On 29.3.52 he was admitted to the Queen Elizabeth Hospital. He rarely talked spontaneously and his reactions to questions or requests were delayed and often inappropriate. Memory was grossly impaired. He was unable to give more than his surname, and said he was 13 years old. He was almost completely disorientated with respect to time, to place and to person, and in addition to a gross apraxia exhibited perseveration in the form of hand and of brow-rubbing. Apart from a B.P. of 200/110 physical examination was negative.

The EEG report stated: "The EEG is grossly and continuously abnormal. Alpha rhythm is almost absent, occurring only sporadically for very short periods in the posterior leads. There is much mixed delta and theta activity from 1·5–3·5 c/s and 4–6 c/s in all leads. This is most marked anteriorly and posteriorly, and is greater on the right side than on the left. The delta waves show phase-reversal at the temporal electrodes on both sides, and frequently occur in short bursts of three or four successive waves synchronously on the two sides in the anterior and posterior leads, followed by longer runs of theta, or mixed theta and delta activity of lower amplitude. The record also shows a small amount of very low voltage fast activity at 20–22 c/s which appears mainly in the left-sided leads."

Ventriculography was performed by Mr. E. A. Turner and showed appearances consistent with gross cortical atrophy. Through the right parietal burr hole a piece of brain was removed for histology (described below).

Cortisone (intramuscular) was then given as follows:

| | | | |
|---|---|---|---|
| 200 | mgm./day | for | 3 days |
| 100 | ,, ,, | ,, | 21 ,, |
| 25 | ,, ,, | ,, | 3 ,, |

After an interval of a week A.C.T.H. was given as follows:

| | | | |
|---|---|---|---|
| 100 | mgm./day | for | 2 days |
| 75 | ,, ,, | ,, | 2 ,, |
| 100 | ,, ,, | ,, | 12 ,, |

and reducing by 20 mgm. per day subsequently.

A second biopsy was taken after administration of Cortisone.

There was no clinical improvement either after Cortisone or A.C.T.H. and the patient was later transferred to an Institution where deterioration continued.

*Case 2.* F.S., female, aged 54, was referred to the O.P.D. of the General Hospital, Birmingham on 4.9.52 with a history of progressive mental deterioration over the past four years. Prior to this she had been a conscientious and efficient housewife who had managed her home and brought up her children successfully. There was progressive confusion and inability to accept responsibility. In the year prior to admission deterioration had been more rapid and she could no longer dress herself or maintain a conversation and her memory for recent events was greatly restricted. She showed none of the restlessness regarded by some as being typical of A.D., and though she had lost the ability to read, she would sit quietly facing an open book which was, as often as not, wrong side up. Physical examination was negative apart from a B.P. of 160/120.

The results of electroencephalography and ventriculography were similar to those on Case 1.

Biopsy was performed as in Case 1. For histology report see below.

Cortisone (intramuscular) was given in the following dosage:

| | | | |
|---|---|---|---|
| 300 | mgm./day | for | 1 day |
| 200 | ,, ,, | ,, | 1 ,, |
| 100 | ,, ,, | ,, | 1 ,, |
| 200 | ,, ,, | ,, | 2 days |
| 300 | ,, ,, | ,, | 3 ,, |
| 100 | ,, ,, | ,, | 30 ,, |

Again there was no clinical improvement and the patient was transferred to an institution where her deterioration continued.

Psychometrics of a formal nature were not possible owing to the gross deterioration of both patients. On the other hand, the few remaining skills offered an excellent base-line to assess improvement.

## HISTOLOGY

The biopsies from both patients showed essentially the same histo-pathology and are therefore described together. They were fixed in 4 per cent. formaldehyde-saline immediately after removal and where possible, fragments were cut off and fixed separately in formol-ammonium bromide. Frozen and paraffin sections were cut, stained by a variety of methods and compared with control sections of normal brain.

The cortex showed focal loss of neurones, marginal gliosis and an increase in intra-neuronal lipo-fuscin pigment ("pigment atrophy"). With silver impregnation abundant senile plaques and neurofibrillary alterations were seen (see Figs. 1 and 2). The plaques had the classical structure described by Critchley (1929), and although present throughout the cortex, were more numerous in the outer layers. The white matter showed axonal degeneration, hyperplasia of astrocytes and mucoid degeneration of oligodendroglia. No definite relation of plaques to blood vessels could be seen.

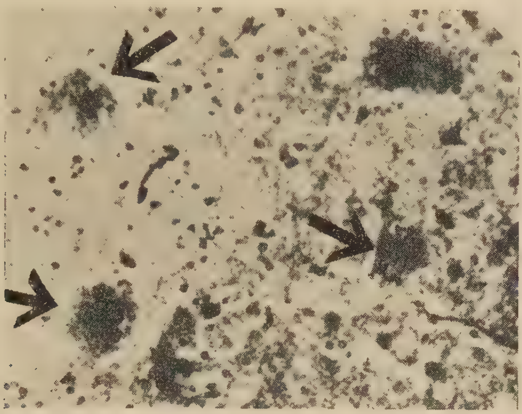

FIG. 3.—Cerebral biopsy showing a positive reaction at the site of the plaques (per-iodic acid-silver method).

Coarsely granular clumps of material staining positively by the per-iodic acid–Schiff technique (P.A.S.) were seen at the site of the argentophile plaques. This granular P.A.S. positive material was amylase fast and was superimposed on a diffuse, P.A.S. positive "background", which corresponded approximately with the size of the plaques seen with silver impregnation. The "background" was more strongly positive than the faint P.A.S. reaction given by the cortical ground substance. A positive reaction at the site of the plaques was also given by the per-iodic acid-silver method for neurones (Dixon, 1953b): this method, like P.A.S., also stained the intraneuronal lipo-fuscin pigment. Substances staining positively with the Alcian-blue stain for mucin, sudan IV (frozen sections) and sudan-black (frozen and paraffin sections) for lipids and the methyl violet reaction for amyloid were less consistently demonstrable. Metachromasia with toluidine blue was also seen at the site of the plaques. Granules of P.A.S. positive material were noted in glial cells, both in the cortex and white matter. The changes appeared to be more marked in the second biopsy of Case 1.

## DISCUSSION

Cortisone and A.C.T.H. had no beneficial effect on the clinical course of the disease in the two patients treated. Our impression was that deterioration was perhaps accelerated by these drugs and the biopsy taken after treatment of patient 1 showed changes which were more marked than those seen before treatment. In a progressive disease one cannot draw conclusions regarding worsening, especially as the histological changes of A.D. may vary quantitatively throughout the brain. Thus an apparent increase could have resulted from chance sampling. In view of recent observations describing enhancement of the production of experimental amyloidosis by cortisone (Teilum, 1952; Peräsalo and Latvalahti, 1954) and as amyloid material has been shown to be present in Alzheimer plaques (Divry, 1927), further attempts to treat A.D. with cortisone would seem to us to be contraindicated.

It is of interest to note the gross EEG changes in both patients. We have noted similar changes in other patients who presented clinical features comparable with those described, only with much less mental deterioration; as biopsies were not performed on these patients, however, the diagnosis of A.D. was not definitely established. It is not possible to generalize on the EEG findings, but there is at least an impression that they may be of early significance. This observation is in accord with that of Delay *et al.* (1944) who reported an absence of alpha waves over areas of cortical atrophy in cases of dementia.

Our histological findings have demonstrated histochemical changes at the site of the plaques. Hiroisi and Lee (1936) found "mucin", and Divry (1927) found "amyloid", and we have noted similar changes in our two cases. The positive P.A.S. and per-iodic acid-silver reactions described seem to indicate the presence of carbohydrate containing material, which appeared to be in excess of that shown by mucin and amyloid stains. Certain non-carbohydrate containing lipid substances, e.g. phospholipids are also said to give a positive P.A.S. reaction and may be present in the plaques. The presence of lipid substances is suggested by our finding that the P.A.S. and per-iodic acid-silver reactions were more strongly positive on frozen sections than on paraffin sections which had been treated with fat solvents. Sudan-black—which stains phosphatide and cerebroside—also gave a stronger reaction on frozen sections. A distinction between the lipid groups was, however, not possible on our material as the limited amount of tissue available from these biopsies restricted further investigation of the question. The staining properties of part of the P.A.S. positive material resembled that of the granules of lipo-fuscin pigment found in cortical neurones (Dixon and Herbertson, 1950, 1951). Dixon (1953a) found similar granular material in phagocytic cells infiltrating necrotic cerebral cortex and suggested that these granules originated in part from lipo-fuscin that had persisted and been phagocytosed after disintegration of neurones.

TABLE I

*Showing the Histochemical Reactions at the Site of the Plaques*

| | Frozen Sections | Paraffin Sections | Significance |
|---|---|---|---|
| 1. Reaction with P.A.S. | ++ | + | Could be due to glycogen, mucopolysaccharide, mucoprotein, glyco *or* phospholipid. |
| 2. Reaction with P.A.-silver | ++ | + | |
| 3. Reaction with P.A.S. after incubation with salivary amylase | ++ | + | Excludes glycogen. |
| 4. Staining with Alcian-blue | | + | Probably mucopolysaccharide present. |
| 5. Metachromasia with toluidine blue | | +− | |
| 6. Metachromasia with methyl violet | | + | "Amyloid". |
| 7. Staining with sudan IV | | +− | Neutral fat present in some plaques. |
| 8. Staining with sudan-black | +(+) | + | Probably glyco or phospholipid present. |
| 9. Prussian blue reaction | | − | No ferric iron. |

An increase in neuronal lipo-fuscin has often been noted in A.D. and it may be that part of the P.A.S. positive material in the plaques originates in the way suggested by Dixon after atrophy of neurones. It also seems possible that the argentophilia shown by the plaques is partly due to the affinity of focal, intracortical deposits of chemical substances for metallic silver. Table I shows that the following substances are probably present at the site of the plaques: neutral fat, "amyloid" material, muco-polysaccharide ("mucin") and glyco- and/or phospho-lipid. The per-iodic acid-silver method (Dixon, 1953b) on frozen sections demonstrates the Alzheimer plaques so clearly that it provides a useful supplementary technique for the rapid diagnosis of A.D. Further studies with modern histochemical techniques are needed and may help to contribute to our knowledge of this disease.

## SUMMARY

Two patients with Alzheimer's Disease, confirmed by cerebral biopsy, did not benefit from treatment with cortisone and A.C.T.H. The histochemical changes are briefly discussed. The per-iodic acid-silver method on frozen sections (Dixon, 1953b) demonstrates Alzheimer plaques clearly.

## ACKNOWLEDGMENTS

We wish to thank Professor P. C. P. Cloake for the EEG reports, Mr. Eric Turner, F.R.C.S., for carrying out the cerebral biopsies, and Professor J. W. Orr for his interest in the pathological investigation.

Part of the histological work was made possible by a grant received from the United Birmingham Hospitals Endowment Fund.

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## ADDENDUM

Since this paper was prepared Corsellis, J. A. N. and Brierley, J. B. have described the histochemical findings in two cases of atypical Alzheimer's Disease (*Brain*, 1954, **77**, 571). In both of these cases an abnormal substance, probably a mucopolysaccharide, was found in the plaque cores, blood-vessels and as free-lying fragments.

# THE PATHOLOGY OF ACUTE INFANTILE CEREBRAL DIPLEGIA

By

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In this paper, the term Acute Infantile Cerebral Diplegia has been used to denote a group of cases in which a spastic paralysis, affecting principally the lower limbs, develops suddenly in infancy or childhood. The course of the disease is remarkably uniform in the majority of cases, thereby suggesting a common pathogenesis.

The malady characteristically supervenes in the course of a febrile illness, especially when accompanied by dehydration, or associated with suppuration in the head or neck. The onset is usually dramatic, with convulsions which may remain unilateral, or occur simultaneously or successively on the two sides and may be preceded or followed by coma. When these acute manifestations have subsided, the patient is found to be paralysed, the legs being predominantly affected, though the arms may be involved to a less extent. In the weeks that follow this initial phase, the legs become progressively more spastic and the patient is often found to be demented. There may be blindness, without loss of the reaction of the pupil to light. From the clinical description of Acute Infantile Quadriplegia by Schlesinger and Welch (1952)—which is probably the same illness as that discussed here—it would appear that the paralysis may occur, on occasion, without preliminary convulsions. The patients may survive for many years, often in hospitals for the mentally defective. During the passage of time, the early brief period of normality comes to be discounted and a diagnostic label of Little's disease is given. It must be emphasized, that the cases under discussion are all normal for several months after birth, a feature which compels their removal from the group of Little's disease. In the latter group, the disease originates in the pre- or para-natal period. The analysis of the pathogenesis in Little's disease is much more difficult than in Acute Infantile Cerebral Diplegia, owing to the complexity of the noxious factors acting on the brain during foetal life and at birth.

Apart from the bilaterality of the paralysis in Acute Infantile Cerebral Diplegia, there is much in common between this disease and Ford's (1952) Acute Infantile Hemiplegia of Obscure Aetiology. The name given to the bilateral condition in this paper has been chosen to stress this similarity. The term Cerebral Diplegia has been used in preference to Bilateral Hemiplegia as it indicates the resemblance of the patient in the chronic phase to patients in the Little's Congenital Cerebral Diplegia group. Bilateral Hemiplegia is usually considered to imply a bilateral, upper motor neurone paralysis affecting upper and lower limbs to an approximately equal extent, while Cerebral Diplegia indicates the predominant involvement of the lower extremities. The term Acute Infantile Quadriplegia, as used by Schlesinger and Welch, describes the state of the patient accurately, but fails to draw attention to its similarity to that of patients with Little's Congenital Cerebral Diplegia.

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* Part of this work was done while holding a Travelling Fellowship from the British Postgraduate Medical Federation.

Although patients with Acute Infantile Cerebral Diplegia differ from those with Ford's Acute Infantile Hemiplegia in rarely being in excellent health at the time of the initial attack, the two diseases resemble one another in the acuteness of the onset, often with convulsions and loss of consciousness, the residual paralysis and frequently associated dementia and the long period of survival with consequent rarity of post-mortem examination. Owing to the lack of post-mortem reports, the pathogenesis of neither condition is completely clear, though Ford suggests that Acute Infantile Hemiplegia is due, in some cases, to vascular lesions and describes a personally observed case with softening of the motor cortex associated with a thrombosis of the superficial branches of the middle cerebral artery.

The object of this paper is to describe the changes in the brains from three cases of Acute Infantile Cerebral Diplegia surviving for many years after the acute stage and to discuss the pathogenesis in the light of these changes. A fourth adult case will be described to illustrate certain points arising from the discussion.

## CASE 1

### *Clinical History*

The patient was a girl born on 23 November, 1928. On 5 June, 1934, she was admitted to Guy's Hospital. I am indebted to the Medical Superintendent of this hospital for the following extract of notes made during the patient's stay there.

The child had been attending out-patients for the previous three years for a variety of complaints, viz. worms, urticaria, bronchitis and tonsillitis.

Between the ages of three and three and a half years, she had many curious attacks, in which she was unable to see, her pupils were dilated and she appeared pale. Her tonsils were removed on 2 May, 1934, following repeated sore throats. On the evening of 4 June, she felt ill and on waking up on the 5 June, her mother noticed a lump on the left side of the neck. She was admitted to Guy's Hospital. On examination, she was very pale and in poor condition. P. 140/min., T. 103° F., R. 30/min. A mass of glands the size of a walnut was visible and palpable in the upper part of the left anterior triangle in the neck. The mass was in part superficial to the sternomastoid, but was not adherent. The throat was inflamed. There was no abnormality in the chest, abdomen or nervous system. On the next day her condition was a little worse. Râles and rhonchi were diffusely present in the chest. The blood urea was 27 mgm. per 100 ml. On the 7 June, the urine contained a trace of albumin, red blood cells, leucocytes, epithelial, hyaline and granular casts. Albumin and blood were observed daily in the urine until the 17 June, after which no further observations are recorded. On the 9 June, the patient's face was pale and puffy, but no oedema was apparent on the legs or back. She had been running an intermittent pyrexia between 97° and 105° F. since admission. Her pulse rate had varied between 100 and 130/min. On the 13 June, the cervical adenitis was subsiding. On the 17 June, a papular rash appeared on the trunk and by the next day, the exposed parts had a blotchy appearance.

In the evening, convulsions occurred on the right side. They were relieved after a few minutes by lumbar puncture, which yielded cerebrospinal fluid under pressure. The fluid contained 2 r.b.c. and 1 lymphocyte per cub. mm. and 15 mgm. per 100 ml. of protein. Chloroform was administered and large quantities of chloral given rectally, after which the convulsions of the limbs ceased. The facial convulsions ceased after about 2½ hours. The next morning, aphasia and extensor plantar responses were observed. By the 21 June, the pulse rate had fallen from 160/min. to 70/min., aphasia was still present and there was a right facial weakness. There was no papilloedema. The cerebrospinal fluid showed 56 r.b.c., 6 lymphocytes and 4 polymorphonuclear leucocytes per cub. mm. There was 45 mgm. per 100 ml. of protein, the Lange curve and Pandy test were normal. An area of tenderness and oedema was present behind the right mastoid process. This is the only reference to the laterality of the oedema, and there is no indication as to the side upon which craniotomy was subsequently performed. These events took place over twenty years ago and it has proved impossible to contact anyone with a clear memory of the case. In view of the right sided nature of the convulsions and the left sided predominance of the cerebral lesions later to be described, it may well be that this note by a medical student was incorrect and that the oedema was in fact on the left side. On the 22 June, Mr. W. J. Ferguson opened up the mastoid air cells (presumably on the left side), explored the middle fossa and made a trephine hole above and posterior to the meatus. The dura was observed to be bulging slightly but there was no extradural abscess. A cannula was passed through the dura towards the motor area. By the 23 June, the pulse was 120/min. but the patient was still febrile and aphasic. Hypertonic saline was administered by rectum. On the 24 June, the temperature fell to normal. On the 2 July, the patient was still aphasic and unable to understand the spoken word. She was incontinent of urine and faeces. On the 13 July, the cerebrospinal fluid showed 4 lymphocytes per cub. mm., 50 mgm. per 100 ml. of protein and 700 mgm. per 100 ml. of chlorides. The patient was discharged to the Fountain Hospital on the 2 August, 1934.

The aphasia and right sided facial weakness persisted and the child altered greatly in personality, becoming dirty in her habits, speaking only in grunts and putting everything into her mouth.

On examination on the 17 August at the Maudsley Hospital (Dr. Mildred Creak), she was seen to be pale and ill, behaved like an idiot and showed an aphasia thought to be predominantly receptive; she did not appear to be deaf and showed no papilloedema or optic atrophy. She was returned to the Fountain Hospital where she was restless and destructive but less faulty in her habits. After two years she developed minor epileptic seizures, in which she gave a jerk and almost fell to the ground. Her mental age remained under one year. She was transferred to St. Lawrence's Hospital, Caterham, where she was described as a low grade imbecile with epilepsy and spastic diplegia, walking with difficulty on her toes. She died of bronchopneumonia, following status epilepticus, sixteen years after the onset of the acute illness.

The post-mortem examination was carried out by Dr. M. K. Beattie on the 22 December, 1950, and I am indebted to her for the following extract from the post-mortem report and for the opportunity to examine the brain and spinal cord.

### *External Appearances*

The body was that of a rather obese young female. The obesity was general and did not show any abnormal distribution. There was marked cyanosis of the fingers, lips and ears.

### *Internal Examination*

Head and neck: The skull was extremely thick. The thickening was irregular, measuring up to ¾ in. There was marked hyperostosis of the anterior and middle fossae of the skull, forming rather smooth, nodular projections and reducing considerably the internal capacity of the cranium. This was most marked on the left side and affected the anterior and middle fossae but not the posterior. The brain which weighed 1,005 gm., was small, corresponding to the reduced capacity of the skull. The olfactory bulbs were removed from narrow recesses in the bone, but were not adherent to the skull. The optic nerve was obscured by the overlapping bone. The brain and spinal cord were fixed uncut. The quantity of cerebrospinal fluid appeared to be excessive. The pituitary was compressed antero-posteriorly. Hypertrophied lymphoid tissue was noted at the back of the tongue and the tonsils were also enlarged. The thyroid was unusually small.

Thorax: The thymus was persistent. The aorta was narrower than normal, but otherwise normal. There was creamy pus in the bronchi, bronchopneumonia in both lungs and a mucocele of the gall-bladder associated with a stone in its neck.

### *Examination of the Brain*

The convolutions of both frontal lobes were narrower than normal. On coronal section, the brain showed marked hydrocephalus of the left lateral ventricle including its inferior horn. The right lateral ventricle was also a little enlarged. The third ventricle was dilated and distended posteriorly so as to form a diverticulum lying dorsal to the pineal gland. There was slight enlargement of the fourth ventricle. The left superior temporal and the superior half of the middle temporal convolutions were markedly atrophic. The white matter of the whole of the left temporal lobe, with the exception of the hippocampal gyrus, was extremely hard and whiter than that of the rest of the brain. The pulvinar of the left side was so foreshortened as to appear absent on coronal section. In a similar way, the left lateral geniculate body did not appear in sections in which the body on the right side was large and prominent. The spinal cord appeared normal. The dural sinuses were not available for examination.

### *Histology*

Frozen sections from the right frontal lobe were stained with scharlach R, Holzer and Gros-Bielschowsky. Frozen sections from each temporal lobe were also stained with Holzer. Blocks were taken for celloidin embedding from the following regions: left and right temporal lobes at two different levels, from the right and left parietal lobes, the left lateral lobe of the cerebellum, the brain stem at all levels and the cervical cord. Sections were stained with cresyl violet, haematoxylin and van Gieson, Loyez, phosphotungstic acid-haematoxylin and Holzer.

### *Findings*

There was dense fibrous gliosis of the white matter of both *frontal lobes* and the *left temporal lobe* (Figs. 1 and 2). The gliosis was least marked around the ventricle. Less severe gliosis was present in the *right temporal lobe*—including sclerosis of the *Ammon's horn*—and the *right parietal lobe*. In the latter, the gliosis was only marked on approaching the Sylvian fissure. In the occipital lobes, gliosis was slight and confined to the digitate white matter. There was severe pallor of myelin staining in the *superior* and *middle temporal convolutions* on the left side and in the dorsal part of the *left frontal lobe* (Fig. 3). There was slight pallor of

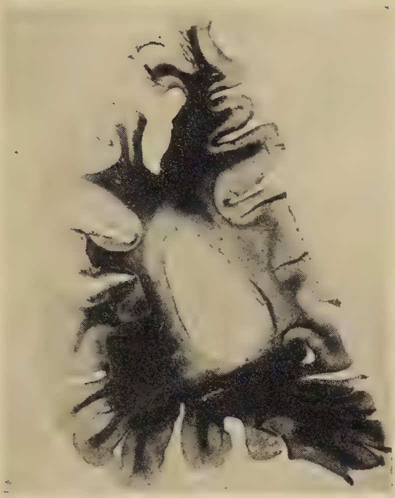

FIG. 1.—Case 1. Right frontal lobe, showing dense fibrous gliosis of the white matter, sparing the periventricular tissue. Frozen section stained with Holzer.

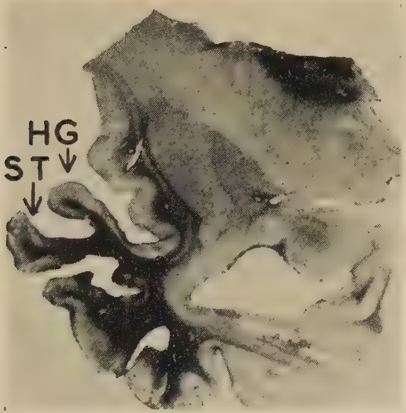

FIG. 2.—Case 1. Left temporal lobe, showing sclerosis and shrinkage of the white matter with ulegyria of the superior temporal convolution and gliosis of the dorso-medial nucleus of the thalamus. Frozen section stained with Holzer.
HG=Heschl's gyrus. ST=Superior temporal gyrus.

myelin staining in the dorsal part of the *right frontal lobe*. The pallor of myelin staining was due to a reduction in myelinated fibres which was paralleled fairly exactly by the loss of axis cylinders. The remaining myelin sheaths were more slender than normal and often showed globular swellings. The axis cylinders appeared normal. Throughout the rest of the brain the myelin was well preserved. Only a very occasional compound granular corpuscle was seen in the Virchow-Robin space in *the frontal lobes*.

Considerable areas of the cortex of the *left temporal and both frontal lobes* showed a laminar sclerosis with status spongiosus of the third layer. The most severe degeneration was found at the depths of the sulci, where complete loss of the normal cortical architecture was encountered. In the anterior part of the *superior temporal gyrus*, there was complete loss of nerve cells from all layers of the cortex, with marked narrowing of the underlying digitate white matter, resulting in ulegyria. Ulegyria was also seen in the *left frontal lobe*, on either side of the sulcus between the *middle* and *inferior frontal gyri*. The gliosis severely affected the capsulae externa and extrema on the left side, but only to a slight extent on the right. There was severe gliosis of the *dorsomedial nuclei of the thalamus* on both sides, with almost total loss

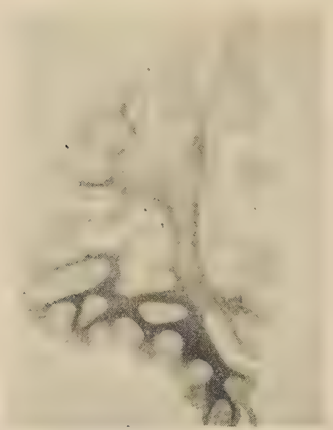

FIG. 3.—Case 1. Left frontal lobe, showing pallor of myelin staining of dorsal part of white matter. Loyez.

of nerve cells. There was a very slight diffuse gliosis of the *globus pallidus* on each side, with accentuation around some of the vessels. The nerve cells and myelin sheaths in the *putamen*, *globus pallidus* and *caudate nucleus* on both sides were normal in appearance. Dilatation of the perivascular (Virchow-Robin) space was more marked around the vessels in the white matter of the frontal lobe than those in the occipital lobe, a few lymphocytes being present between the collagenous fibres.

### CASE 2

*Clinical History*

This child was born normally at term, and, though kept for a long time in a "warm bed", developed normally until the age of nine months, when high fever and convulsions developed

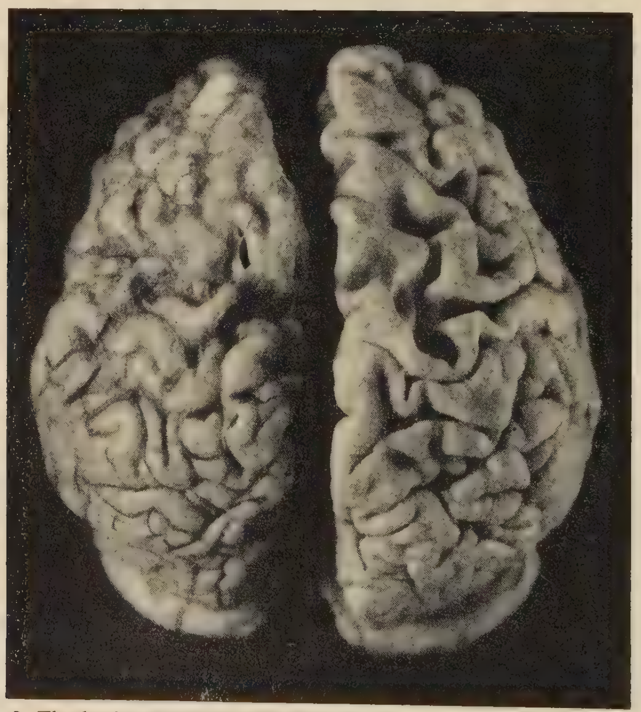

FIG. 4.—Case 2. The brain viewed from above showing atrophy of the dorsal parts of both cerebral hemispheres.

suddenly in the course of an otitis media. The child remained for six months in the Children's Clinic in Leipzig, but failed to make any further progress, never sitting up or being able to talk. He was transferred to a home and then, at the age of 5 years, to the Landesanstalt at Chemnitz-Attendorf, where he was found to be in poor general condition with his body extended and rigid, though it was possible to move the limbs passively without spasm occurring. The tendon reflexes were slightly increased. No further convulsions occurred. The child was quite unclean, apathetic, and frequently burnt himself. He made no further mental progress and died at the age of six years from acute tonsillitis and lobar pneumonia.

No details are available as to the findings at autopsy, but through the kindness of Professor W. Scholz, I am able to give the following details of the examination of the brain which was carried out at the Deutsche Forschungsanstalt für Psychiatrie in Munich.

### *Examination of the Brain*

The brain, which was fixed in formalin, weighed only 380 gm. Both cerebral hemispheres appeared to be normally developed, but were severely atrophic so that there was gaping of the sulci between convolutions which were firmer than normal. These changes were most marked on the mesial and basal aspects of the occipital lobes, but were also prominent further forward on the dorsal aspects of the frontal and parietal lobes (Fig. 4). There was marked dilatation of the lateral ventricles, especially in the region of the posterior horns. The ependyma was smooth. The corpus callosum was normally formed but extremely thin. In coronal sections through the frontal lobes, the cortex was narrowed, especially in the depths of the sulci. The white matter was shrunken and harder than normal, but retained its white colour. The basal ganglia appeared normal to the naked eye. The white matter of the cerebellar hemispheres was very hard and yellow, and the foliae appeared atrophic.

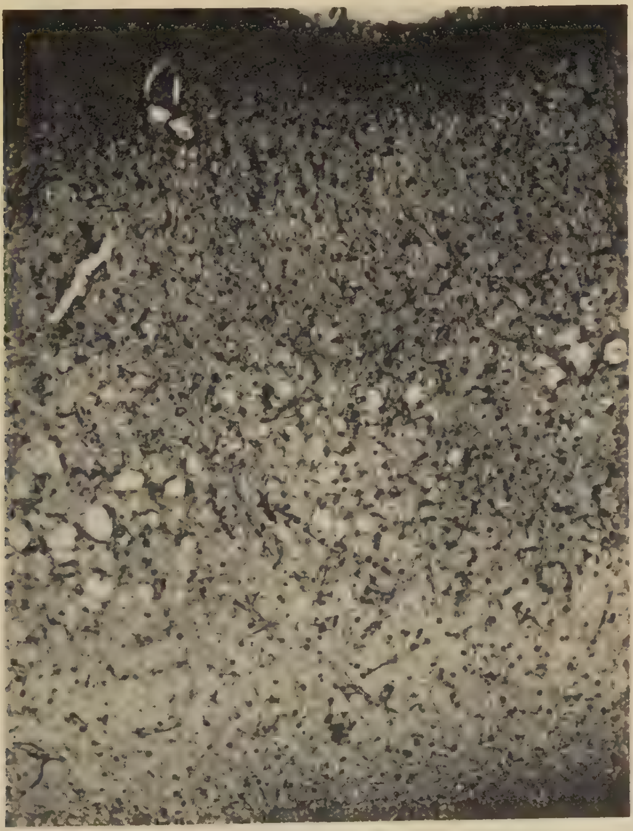

FIG. 5.—Case 2. Basal region of occipital lobe, showing dense gliosis of cortex, with status spongiosus of the third layer. Frozen section, stained with Holzer. ×100.

*Histology*

Blocks were taken from the basal part of the occipital lobe, through the entire cerebral hemisphere at the level of the optic tract, the central region, the frontal lobe and the cerebellum. Frozen sections were stained with Holzer and Spielmeyer and celloidin sections with Nissl.

*The basal region of the occipital lobe* showed complete destruction of the cortical architecture with status spongiosus in the third layer. There were many compound granular corpuscles both in the perivascular spaces and disseminated through the cortex. There was a dense gliosis of the cortex with accentuation, both in the superficial layers and around the spaces in the spongy third layer (Fig. 5). The white matter showed a uniform, moderately severe, diffuse pallor of myelin staining, with slightly less pallor of the optic radiation. With higher magnification, the myelin sheaths were seen to be reduced in number and showed at intervals, globular or fusiform swellings or a varicose outline. There was a very dense, uniform, fibrous gliosis throughout the white matter. There were numerous fat-laden compound granular corpuscles in the Virchow-Robin spaces, but none elsewhere in the white matter. There were also moderate numbers of lymphocytes in the Virchow-Robin spaces, but the latter were not notably dilated, though the space of His was unusually wide. There was a marked increase in the astrocytic nuclei, which were of normal form, and there was a moderate diffuse increase in microglia. A section through the *hemisphere at the level of the optic tract* showed a less dense though still marked fibrous gliosis affecting the lateral part, and especially the digitate white matter, of the parietal lobe, with a very slight gliosis of the rest of the white matter (Fig. 6). The dorsal part of the parietal lobe also showed a marked fibrous gliosis of the upper two layers of the cortex and status spongiosus of the remaining layers.

*Central region:* Few nerve cells remained in the cortex, but those present had a normal appearance. There was an increase in astrocytes, some of which were hypertrophic. Formation of glial fibres in the cortex was only slight, but a status spongiosus was present. In the white

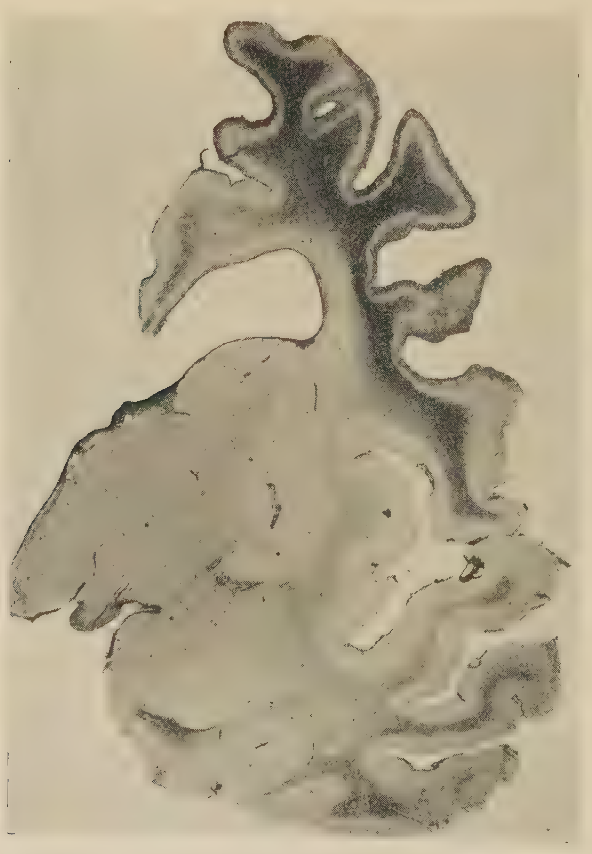

FIG. 6.—Case 2. Section through cerebral hemisphere at level of optic tract, showing fibrous gliosis of dorsal part of hemisphere, largely confined to white matter. Frozen section stained with Holzer.

matter there was a moderately dense fibrous gliosis. Pallor of myelin staining was only slight, but the myelin sheaths were reduced in number and those remaining showed beading and varicosity. Moderate numbers of compound granular corpuscles were disseminated throughout the cortex and concentrated around the vessels in the white matter. In the *frontal lobe*, there was marginal gliosis in the cortex, with a moderately severe fibrous gliosis of the superficial two layers and status spongiosus of the deeper layers, as in the occipital lobe, though more moderate in degree. Over the most severely affected areas of cortex, the arachnoid was thickened and contained mononuclear cells in its interstices. *Insula:* There was an occasional nerve cell with homogenizing cell change. *Ammon's horn:* There was marginal gliosis of the hippocampal gyrus and gliosis of the subiculum. There was status spongiosus and extensive outfall in cells from Sommer's sector. *Cerebellum:* In the atrophic foliae, the molecular layer was very shrunken and the granular layer was reduced to a narrow strip. The molecular layer showed a dense fibrous gliosis, in the midst of which many Purkinje cells remained, though others had disappeared, their former situation being indicated by a focal proliferation of the Bergmann cells (Fig. 7). There was also a severe fibrous gliosis of the white matter and dentate nucleus.

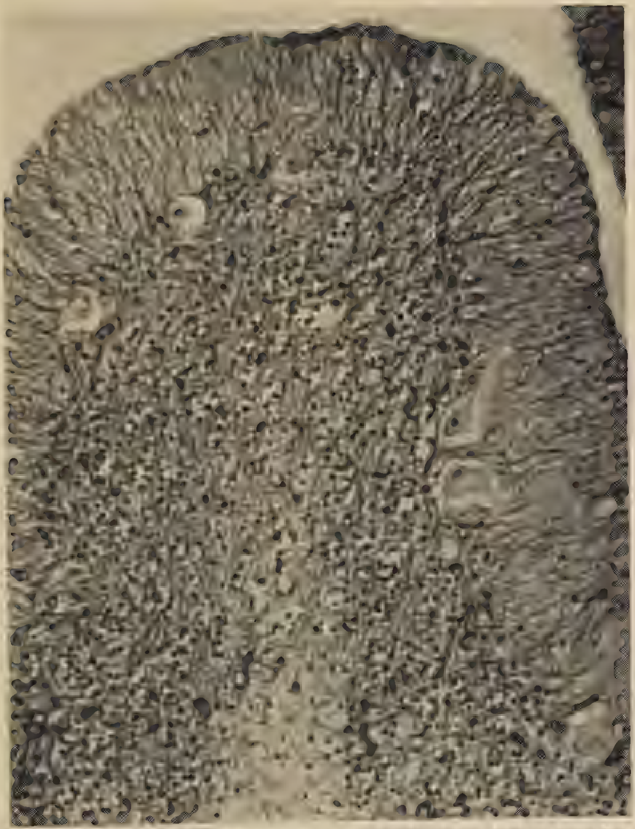

FIG. 7.—Case 2. Lateral lobe of cerebellum, showing gliosis and atrophy of molecular layer, with persistence of many Purkinje cells. Frozen section, stained with Holzer. × 180.

I am indebted to Dr. Ludo van Bogaert for permitting me to report Case 3 which was investigated by him at the Institut Bunge, Antwerp.

## CASE 3

### *Clinical History*

The patient was a boy aged seven years when he first came under the care of Dr. van Bogaert. He was the youngest of six children. His birth had been normal, and, apart from whooping cough at the age of a year and a half, he had been in good health until he was three.

At the age of three years and one month, a chill was followed by severe pneumonia commencing on one side but becoming bilateral. There was severe cyanosis and it was thought unlikely that he would recover. However, on the ninth day his condition improved. Several days later, he had pyuria with occasional febrile episodes. Twenty days after his temperature returned to normal, he suddenly became comatose and then developed convulsions. Ten days later, consciousness returned, but he was found to have paralysis of all four limbs and was blind. He was subsequently admitted to the Bachten Mental Hospital under Dr. Devos, where there was found to be a spastic quadraplegia with choreoathetoid movements of the toes. The lower limbs were in extension and crossed scissor fashion and there were contractures in extension of both big toes. The upper limbs were half flexed and half pronated, the fist was in line with the forearm, the fingers were spread out and showed occasional involuntary movements. There was no wasting. He was completely demented and uttered no sound. He swallowed normally. He was completely blind. The pupils were dilated but reacted to light. The optic fundi were normal but there was a pericapillary pigmented zone and abnormal pigmentation of the macula. The following year, the upper limbs became flexed but the lower limbs remained as before. There were frequently a series of rhythmical movements of the head to the right or left, two or three movements being made in a minute; these movements were accompanied by rhythmical contraction of the orbicularis oculi with the same frequency. Lumbar puncture yielded a fluid containing 3 cells per cub. mm. and 20 mgm. protein per 100 ml. The Wassermann reaction was negative both in the blood and the cerebrospinal fluid. The patient died of bronchopneumonia at the age of eleven years.

Only the brain was available for study.

### *Histology*

Blocks were taken so as to incorporate the dorsal half of one hemisphere at the level of the anterior and centromedian nuclei of the thalamus respectively and also from the dorsal half of the occipital lobe. Frozen sections were taken from these blocks and stained with Holzer and Spielmeyer. Celloidin sections from a block incorporating an entire hemisphere, cut in the coronal plane through the centromedian nucleus, were stained with Nissl. Sections taken from a block obtained by sagittal section of the other hemisphere in the sagittal plane, were stained by Weigert-Pal.

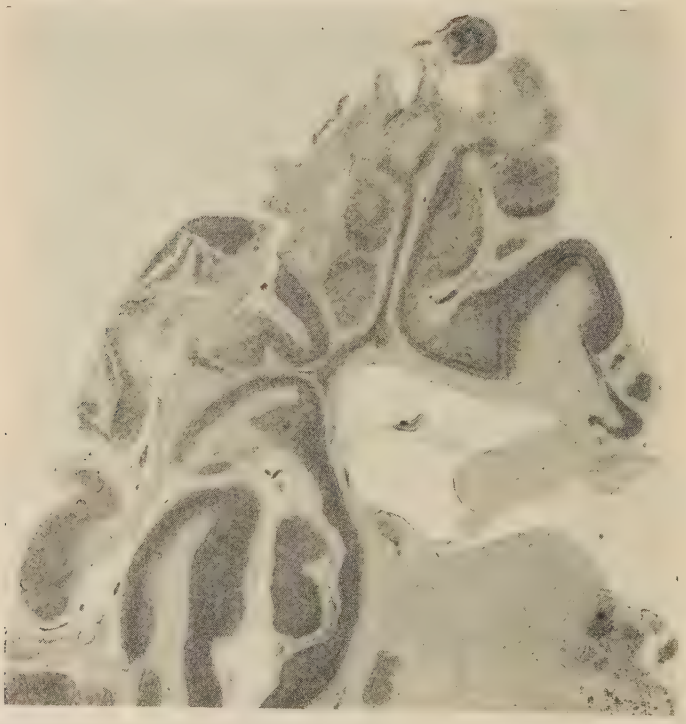

FIG. 8.—Case 3. Parietal lobe, showing ulegyria and the narrow, centrally placed line of dark staining in the digitate white matter. Note ulegyria of Heschl's gyrus. Nissl. ×2½.

*Findings*

The severest changes were confined to the *parietal* and *occipital lobes* on the two sides and were symmetrical. The gyri on the lateral aspect of the hemisphere dorsal to the Sylvian fissure, together with the posterior part of the *superior temporal convolution*, were, for the most part, ulegyric with almost complete destruction of the cortex, which was reduced to a narrow band of glial tissue. The underlying white matter was greatly shrunken and, in Nissl preparations, showed with the naked eye a central line of dark staining due to the increase in astrocytic nuclei and processes (Fig. 8). Passing further forward to the level of the *centromedian nucleus of the thalamus*, the cortex was seen to be intact except for the tip of the two most dorsal convolutions, where gliosis continued from the shrunken white matter through a cortex atrophic at these points only. There was a diffuse pallor of myelin staining in the deeper part of the digitate white matter and the greatly shrunken centrum semi-ovale, just external to the lateral angle of the ventricle, showed an approximately pentagonal area of complete destruction of myelin, the greatest breadth of which was 0·4 cm. Laterally, the border of this area was sharp, but mesially, towards the corpus callosum, many palely staining, irregularly swollen sheaths crossed the border so as to make the latter less distinct. This area could still be seen in sections through the *anterior nucleus of the thalamus*, but the pallor of myelin staining was no longer complete. The demyelination was accompanied by a fibrous gliosis of loose texture. At this level, there was still more severe shrinkage of the white matter of the centrum semi-ovale and of the most dorsal convolutions and the convolutions dorsal to the Sylvian fissure on the lateral aspect of the brain. The *cingulate* and *paracentral gyri* appeared normal, but the *precentral gyrus* showed marked shrinkage and pallor of myelin staining, with moderate gliosis of its white matter, though the cortex was not atrophic. The two more ventral convolutions, however, showed ulegyria, with more severe gliosis and shrinkage of the white matter. The section cut in the sagittal plane and stained with Weigert-Pal, showed that the deep white matter beneath the ulegyric convolutions at the *occipital pole* was completely demyelinated and that some pallor of myelin staining was present in the centrum semi-ovale as far forward as the frontal lobe.

## COMMENT

These three cases, which show between them most of the important features of Acute Infantile Cerebral Diplegia, present many points of similarity with a case reported in 1937 by Bailey and Hass, in which the superior longitudinal sinus was found at autopsy to be completely occluded in its middle half by organized thrombus. The case was that of an infant, who, in the course of an attack of diarrhoea at the age of four weeks, suddenly became flaccid, as if dead, and shortly afterwards had a convulsion lasting twenty minutes. Three similar seizures followed within an hour. The temperature was 105° F. Another convulsion occurred on admission to hospital, when the lower extremities were noted to be held rigidly. After a week, he was sent home, where he had one to three seizures daily. At two months the head measured 16½ in. in circumference. The arms and legs were rigid so that he could support his weight on his legs. The cerebrospinal fluid was xanthochromic and contained red blood cells. There was hydrocephalus. He died from gastroenteritis at three and a half months. The similarity between this clinical history and that of our three cases, suggests that the latter may also have suffered a thrombosis of their superior longitudinal sinuses. If this vessel had been available for histological examination in the cases reported in this paper, this possibility could easily have been tested and if the opportunity for making such an examination in similar cases were likely to present in the near future, there would be little excuse for writing this paper. However, opportunities for carrying out post-mortem studies on cases of Acute Infantile Cerebral Diplegia in the chronic stage rarely present and when they do, examination of the dural sinuses is apt to be superficial. Organized thrombi in the sinuses are often inconspicuous and it may be useful to illustrate with an example (Fig. 9) from the straight sinus of a child who had a febrile episode heralded by convulsions at three weeks and died aged ten months at the Hospital for Sick Children, Great Ormond Street. The inconspicuousness of the resultant fibrous nodule emphasizes the need for histological confirmation in such cases.

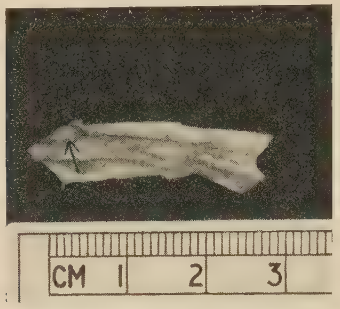

FIG. 9.—Organized thrombus (arrow) in the straight sinus of a child dying 9 months after the probable onset of the thrombosis.

It seems, therefore, worthwhile examining the evidence for and against an origin for the cerebral diplegia in thrombosis of the superior longitudinal sinus, in our three cases.

Firstly, we may consider the antecedent conditions and the clinical course. In Case 1, there was cervical adenitis following tonsillectomy, Symonds (1937) has reported a non-fatal case (his Case 2) in which he considered that thrombophlebitis of the right lateral sinus had arisen from a peritonsillar abscess and spread to the superior longitudinal sinus and thence into one of its tributaries draining the right precentral cortex. He thought, following Goldman (1936), that the thrombotic process had started in the jugular vein. Courville and Nielsen (1935) have indicated the not infrequent spread of otitic thrombophlebitis of the lateral sinus to the superior longitudinal sinus *via* the vein of Labbé and the superior anastomotic and superficial middle cerebral veins. The clinical features in Case 1 are fully consistent with a spread of thrombosis in this way to the superior longitudinal sinus from the left jugular vein. The neurological symptoms were ushered in by convulsions indicating a lesion of the precentral gyrus near the Sylvian fissure on the left side. Oedema over the mastoid process indicated the probability of thrombosis of the lateral sinus with interference with the blood flow in the mastoid emissary veins. The pulse rate fell in three days from 160 to 70 per minute although the patient remained febrile. At operation the dura was bulging. Thus there appeared to be raised intracranial pressure, though there was no papilloedema as was seen by Bailey and Hass in their first two cases of thrombosis of the superior longitudinal sinus. Whatever the process responsible for the convulsions was, it appeared to be capable of spontaneous arrest, as the intracranial pressure returned to normal and the patient became ambulatory, though spasticity in both lower limbs continued to develop for several years, while her intellectual status was that of idiocy and she subsequently became afflicted by minor epileptic seizures.

In Case 2, the convulsions at the onset were associated with otitis media and accompanied by high fever. The association of thrombosis of the lateral sinus with otitis media is classical and the same route of spread to the superior longitudinal sinus can be envisaged as that just mentioned. The state of the patient in the chronic phase was similar to that in Case 1, with the additional involvement of the arms.

In Case 3, coma and convulsions, followed by a spastic quadraplegia, occurred ten days after a pyuria of unknown origin. Here we may recall Symond's (1937) case (7), where he suggested that thrombosis of the superior longitudinal sinus had followed a thrombophlebitis migrans, probably secondary to a perirectal abscess. Some form of pelvic suppuration may have been present in Case 3, spread of the thrombosis occurring from the pelvic veins to the dural sinuses as a thrombophlebitis migrans or as venous thromboembolism *viâ* the vertebral venous plexus as postulated by Batson (1940, 1942).

Thus all three cases of Acute Infantile Cerebral Diplegia have a clinical history consistent with venous thrombosis spreading to the superior longitudinal sinus. It is intended now to show, that the changes found in the brains from these cases are equally in accord with such a pathogenesis.

The changes in the brains from each of the three cases were strikingly similar. In each, there was a very severe and diffuse sclerosis of the white matter of the dorsal parts of the two cerebral hemispheres. The area of sclerosis was poorly demarcated, fading gradually into the surrounding tissue. While in Case 1, the frontal and left temporal lobes were the most severely affected, in Cases 2 and 3, the occipital lobes had suffered most. The sclerosis was accompanied by a much milder pallor of myelin staining. There was little evidence of the products of the breakdown of myelin, which form so prominent a feature in cases of classical "Diffuse Sclerosis". In the most atrophic areas, there was evidence of loss of nerve cells and cortical degeneration varying in severity through laminar sclerosis up to complete atrophy and ulegyria.

Sclerosis of the white matter in excess of demyelination is an interesting pathological change. Similar demyelination, but without notable gliosis has been described in oedematous areas around cerebral tumours by Greenfield (1939). The absence of gliosis in these cases of cerebral tumour is probably due to the short duration of survival after the onset of the oedema. Thus, only in animals surviving ligation of the superior longitudinal sinus by more than two months, does fibrous gliosis appear and become increasingly dense (Putnam, 1935; Woolf, 1954). These changes were attributed by the latter author to oedema resulting from venous stasis. Scholz (1949) has shown, in cases dying from thrombosis of the superior longitudinal sinus in the acute stage, that the area in which the effects of oedema can be observed is more extensive than that showing the effects of anoxia. While oedema principally affects the myelin sheaths, the nerve cells are most susceptible to anoxia. This was found to be the case in the animals with ligation of the superior longitudinal sinus, where, in the presence of a widespread diffuse gliosis, only the cortex adjacent to the sinus was degenerated. The prominence, though not dominance, of atrophic changes in the cortex in our three cases, suggests that if these lesions were, in fact, due to a thrombosis of the superior longitudinal sinus, then a considerable degree of anoxia must, on occasion, accompany the oedema in the areas with the greatest degree of venous stasis. The anoxia, cannot, however, be of the severity present in most cases of arterial obstruction since none of the three cases showed softening of the brain, a feature present in the vast majority of cases, where the supply rather than the return of blood is impeded.

In the literature, haemorrhagic infarction with softening is frequently regarded as the typical sequel to thrombosis of the superior longitudinal sinus. While this may be correct for the rapidly fatal cases, it is certainly not so for cases surviving for longer periods. A case studied at The Hospital for Sick Children, Great Ormond Street is illustrative of this point. The patient was a child aged thirteen months suffering from an obstructive hydrocephalus. Its lateral ventricles were drained into the pleural cavity. Aspiration of the fluid that accumulated in this cavity was followed by extensive cerebral venous thrombosis, which was shown at autopsy, a month later, to have affected the anterior third of the superior longitudinal, the straight and both transverse sinuses and to have spread into the veins on the convexity of the left hemisphere (Fig. 10), the thrombosis having apparently started in the transverse sinus and spread into the vein of Labbé in the manner suggested by Courville and Nielsen.

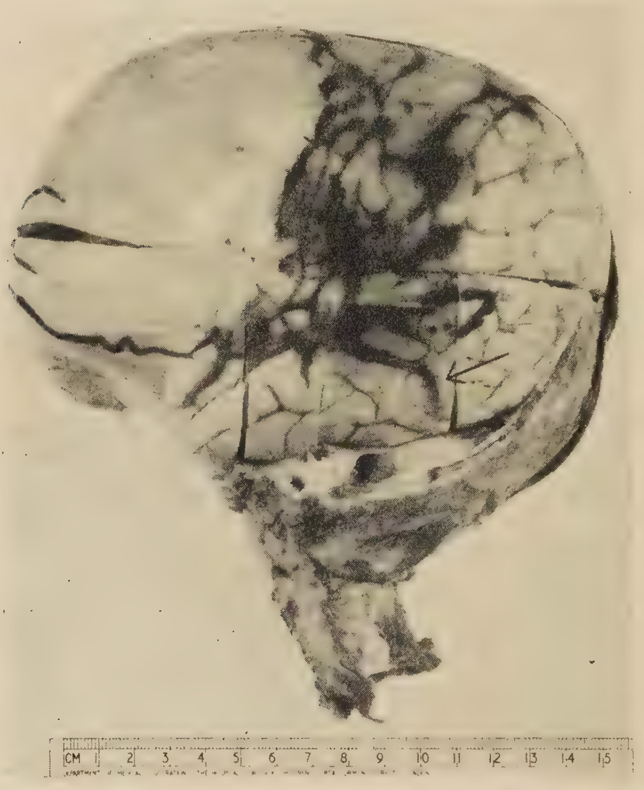

FIG. 10.—Hydrocephalic brain, showing thrombosis spreading on the convexity of the brain from the transverse sinus *viâ* the vein of Labbé (arrow) to the superior longitudinal sinus. Note thrombosed vein coursing across the ventral part of the frontal lobe. The thrombosis occurred three weeks before death.

The great vein of Galen and both internal cerebral veins were thrombosed. In spite of this extensive involvement of the venous system, as well as the additional embarrassments of a left subdural haematoma and the hydrocephalus, infarction visible with the naked eye was confined to a softening the size of a pea deep to one of the pre-Rolandic veins on the convexity of the hemisphere. There was, however, severe haemorrhagic infarction of the basal ganglia on the left, but this was no doubt due to the thrombosis of the Galenic system and could not be attributed to the thrombosis in the superior longitudinal sinus or its branches.

The method of spread of the thrombophlebitic process, so clearly illustrated in this case, would explain very completely the distribution of the lesions in Case 1, the severe affection of the left temporal lobe corresponding to thrombosis of the overlying vein of Labbé.

Before leaving this illustrative case, attention should be drawn to the thrombosed vein coursing across the convexity of the ventral part of the left frontal lobe. This vein ran into a short, unnamed, dural sinus passing just above the orbit, which finally emptied into the anterior part of the superior longitudinal sinus. Oedema over the orbit was a valuable diagnostic feature in this case and was probably due to obstruction of diploic veins draining into the unnamed sinus. Similar obstruction of diploic veins may have a bearing on the extremely thick calvarium over the anterior and middle fossae in Case 1.

The pentagonal focus of demyelination and gliosis seen in the centrum semi-ovale, adjacent to the lateral angle of the ventricle in Case 3, is of interest since it suggests a milder degree of the paraventricular softenings reported by Norman (1953) as possibly resulting from thrombosis of the great vein of Galen. There were, however, in Case 3 none of the lesions in the basal ganglia usually associated with thrombosis of the Galenic venous system. However, these lesions need not follow obstruction of this system as was suggested by Bedford's (1934a, b) experiments in which he placed a clip on the great vein of Galen and particularly strikingly demonstrated by the following case in which thrombosis of this vessel was an unexpected post-mortem finding. This case has the additional interest of showing that cerebral oedema due to obstruction of cerebral veins may produce its effects wholly unaccompanied by the effects of anoxia and in this way resemble exactly the oedema associated with cerebral tumours.

## CASE 4

### *Clinical History*

The patient, a man aged forty-seven, was admitted to the Bethnal Green Hospital on the 24 May, 1951. The details of the clinical history are not relevant to the subject under discussion and we need only mention that he died a few days after developing pneumonia. Post-mortem examination showed sub-acute bacterial endocarditis with mitral stenosis.

### *Examination of the Brain after Fixation in Formalin*

The brain was large, weighing 1,570 gm. The ventricles were not enlarged. The vessels at the base of the brain were a little more rigid than normal, but showed no obvious atheroma. The posterior cerebral artery was opened up on the left side, its lumen was patent and it contained no embolus. On opening the great vein of Galen, a whitish, cord-like, adherent thrombus was seen to occlude the lumen almost completely. Anteriorly, extensions of the thrombus were seen to pass into the internal cerebral veins. They were, however, not adherent to the walls of the vessels. There was marked uncinate herniation, more marked on the right than on the left. There was also marked tonsillar herniation. The ventral part of the *left occipital lobe* showed a greyish discoloration of the digitate white matter, within which were numerous, distended, small veins which were filled with fresh blood clot (Fig. 11). The adjoining cortex, which was

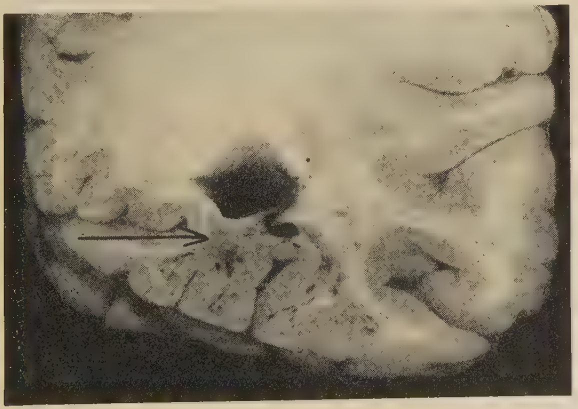

FIG. 11.—Case 4. Occipital lobe, showing area of greyish discoloration (arrow) in white matter, with sparing of the cortex.

separated from the greyish white matter by apparently intact, subcortical fibres, appeared macroscopically normal. Passing anteriorly, there was seen to be a crescentic cleft embracing the white matter beneath the *collateral sulcus* on the left side. The cleft was filled with a gelatinous fluid and ante-mortem clot and was narrowly separated from the cortex by sub-sulcine "U" fibres. The veins lining the left posterior horn were very distended and one of them obviously communicated with the cavity described. On dividing the slab, which contained the cavity, into two, by a further coronal section, a fusiform, ante-mortem blood clot 0·7 cm. long ×0·3 cm. wide was seen to lie within the collateral fissure. As it extended towards the surface it tailed off into a cord-like structure, apparently an obliterated vessel. Following it inwards, it was seen to be continuous with the clot in the cavity described above.

### *Histology*

Frozen sections were taken from the ventral portion of the left occipital lobe and stained with scharlach R, Holzer, and the Takiya-Siko modification of Weigert-Pal. Frozen sections were also impregnated by Penfield's modification of Hortega's method for microglia. Blocks were also taken from the dorsal and ventral portions of each occipital lobe, from both central regions, both frontal and temporal lobes, both lentiform nuclei and at five levels through the thalamus. These blocks were embedded in celloidin and sections stained with haematoxylin and van Gieson, cresyl violet and phosphotungstic acid-haematoxylin. Sections through the left occipital lobe were also impregnated with Gros-Bielschowsky.

### *Findings*

Sections through the great vein of Galen showed that the thrombus it contained had been completely converted into fibrous tissue and was densely adherent to the wall of the vein. Sections through the ventral part of the occipital lobes showed that the veins in the white and grey matter were very distended, especially on the left. The distension was most marked in the white matter of the left fusiform gyrus. An occasional vein, in the white matter, was completely occluded by a fibrous plug. The veins immediately medial to the inferior horn of the lateral ventricle, were very distended and some of them had necrotic walls and were surrounded by red blood cells. One small vessel—probably an arteriole—was surrounded by a homogeneous material staining like plasma. It contained a few clumps of red blood cells (Fig. 12). Throughout the white matter of the ventral part of the occipital lobe, frozen sections showed swelling and beading of the myelin sheaths, with formation of free-lying globules of myelin. The cortical myelin sheaths were tortuous and varicose, otherwise the cortex was little affected. The axis cylinders were displaced by the dilated veins, but were not swollen. There were occasional twinning astrocytes and a conspicuous lipofuscin content of both astrocytes and nerve cells. In cortex and white matter, there was hypertrophy of microglial cells without any great increase in their number. Phagocytes containing fat were never seen, but some of the distended veins in the white matter contained large globules of neutral fat. The astrocytes in the white matter were considerably increased in number especially along the course of the vessels. They frequently showed regressive changes, the nuclear chromatin being arranged around the periphery of the nucleus under its membrane and staining more darkly than usual. The cytoplasm was bulky, ragged, stained palely and often contained large vacuoles. Eventually

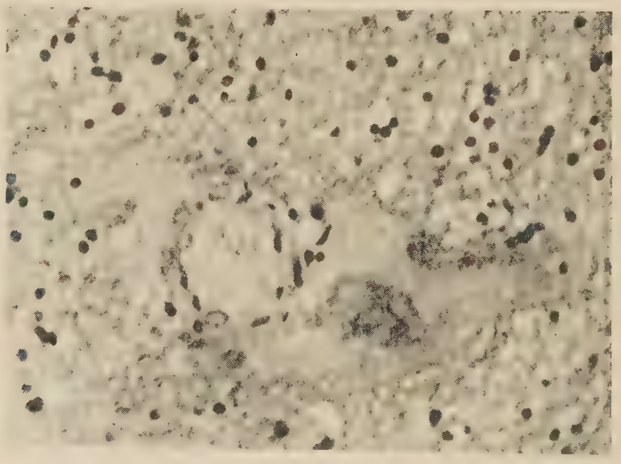

FIG. 12.—Case 4. Section from discoloured white matter, showing perivascular exudate. H. van G. ×350.

the nuclei of these cells shrank, became very pale and finally faded away completely. A few astrocytes appeared activated and there was a light formation of glial fibres. The oligodendroglial cells were pyknotic but showed no other abnormality. The rest of the brain including the Ammon's horn and cerebellum was normal.

## COMMENT

In this case, the thrombosis of the great vein of Galen probably occluded the entrance of the periventricular veins draining the ventral portion of the occipital lobe. The vein was probably never completely occluded as the basal ganglia were unaffected. The greyish discoloration of the white matter was due to a degeneration of the myelin sheaths with only an insignificant gliosis. Presumably a more prominent gliosis would have occurred if the patient had survived longer.

Degeneration of the myelin sheaths without formation of compound granular corpuscles is characteristic of "oedematous necrosis" (Jacob, 1940). While the changes in this case fall short of necrosis—in spite of the regressive changes in the astrocytes—the presence around the veins of a homogeneous material, staining like plasma is practically diagnostic of oedema. Exudates with a similar appearance were reported by Jaburek (1935) in oedematous areas near cerebral tumours, but the histological effects of oedema may occur without any stainable perivascular exudate as Greenfield (1939) has shown and as Woolf (1954) found in animals whose superior longitudinal sinus had been ligated experimentally. Scholz (1949) has related the unstainability of such exudates to their low content of protein. It may, of course, also be that the exudates were present at the time when the oedema was developing but had been absorbed during a period of dehydration, immediately before death, without sufficient time elapsing for the swelling of the myelin sheaths to subside. The presence of globules of sudanophil material in the greatly dilated veins is of interest in that it suggests that the products of the breakdown of the myelin sheaths were being transported towards the vessels by a humoral mechanism, emulsification occurring in the excess of fluid in the tissue spaces and then passing, in the form of globules too small to demonstrate by staining, through the perivascular space and vessel wall into the lumen of the vessel. Here they coalesced with the production of globules of demonstrable size. Probably the latter would never have been seen were it not for the stagnation of flow in the veins, consequent upon their obstruction by the thrombosis.

What is of particular importance in this case is the complete absence of degeneration of the nerve cells in the cortex overlying the discoloured white matter. While it is tempting to see in this absence of anoxic effects, a striking confirmation of Scholz's postulation that oedema is always more extensive than anoxia in cerebral venous obstruction, it may also be related to the territory normally drained by the periventricular veins, which may not include the cortex.

The area of greyish discoloration in the white matter in this case may well represent an early stage in the development of the gliosis seen in Cases 1 to 3, but to find lesions comparable with this more severe sclerosis, cases surviving for longer periods must be studied.

There do not seem to be in the literature any cases of this nature, where survival was long enough to enable sclerosis to develop and where the pathological investigation was sufficiently meticulous to allow such changes to be demonstrated. In several cases, such as Russell's (1949) Cases 46 and 47, attention was focussed on areas of haemorrhagic infarction and the possibility of an extensive sclerosis and demyelination, of the type seen in our Cases 1 to 3, existing beyond the borders of the infarcts, cannot be excluded. Indeed, in reference to the haemorrhagic infarction in the right cerebrum of her Case 47, Russell refers to a peripheral zone of early gliosis.

Hallervorden (1939) reported the case of a boy aged 2¼ years whose birth was said to have been premature and to have been followed at a short interval by epilepsy and then by a spastic paralysis of the right arm and both legs. Just before he died, from a lung inflammation, there were convulsions of the left side and face. At autopsy, there were old changes in the left parasagittal region with extensive shrinkage of the cortex, with laminar destruction, and atrophy of the white matter. The accompanying microphotograph showed a diffuse demyelination of the atrophic white matter. Unfortunately, there is no note as to whether the demyelination, which closely resembled that seen in Cases 1 to 3, was accompanied by a similar sclerosis or whether there was the same inconspicuous formation of compound granular corpuscles. There was an organized thrombosis of the superior longitudinal sinus, occluding the left superior cerebral vein. A remarkably similar case, also with symptoms dating from the neonatal period, was described in greater detail by Norman (1936).

These cases strongly suggest that the changes in Cases 1 to 3 were also due to thrombosis of the superior longitudinal sinus.

Thus a considerable amount of evidence has been put forward in favour of an origin of Acute Infantile Cerebral Diplegia in thrombosis of the superior longitudinal sinus. It is not suggested that thrombosis of this vessel only produces lesions of the type seen in Cases 1 to 3. It will, in fact, be shown in a paper to be published later, that liquefactive changes may dominate if the thrombosis occurs in the first few weeks of life. Russell's cases show that "healed" softenings may be the most striking feature. There seems no doubt, however, that the morbid anatomical syndrome of sclerosis and demyelination of the white matter drained by the thrombosed sinus may occur with great purity, i.e. with little or no involvement of the overlying cortex and without even incomplete softening.

Although no other cause for Acute Infantile Cerebral Diplegia seems as likely as thrombosis of the superior longitudinal sinus, it must be admitted that the changes seen in the brains from our three cases, resemble closely lobar sclerosis, which has recently been postulated by Scholz (1951) as one of the sequelae of convulsive seizures in childhood. It must be pointed out, however, that although there is good evidence that patchy palings may be found in the cerebral cortex as an immediate sequel to epileptic seizures (Meyer, 1939), there is far less certainty that lobar sclerosis is, in fact, the result and not the cause of epilepsy.

Sclerosis of the cerebellum in Case 2, might be put forward more confidently as a result of the epileptic seizures, although in this case the convulsions do not appear to have persisted beyond the acute stage. Furthermore, the cerebellar involvement may have been due to an extension of the thrombosis into the straight sinus. Softening of the vermis of the cerebellum may result from thrombosis of the straight sinus in the first month of life, and did, in fact, occur in the case illustrated in Figure 9. Possibly a similar obstruction later in life would have resulted in a more sclerotic lesion.

It must also be pointed out that while an origin in thrombosis of the superior longitudinal sinus explains the convulsions as well as the changes in the brain, a dependence of the lesions upon the convulsions leaves the origin of the seizures in obscurity. It is, of course, possible, or even probable, that convulsions occurring in the chronic stage of Acute Infantile Cerebral Diplegia aggravate and extend the lesions in the brain.

In conclusion, it must be emphasized that cerebral diplegia is not the only possible sequel to thrombosis of the superior longitudinal sinus and it may not be inappropriate to quote again after more than twenty years, the concluding words of Byers and Hass (1933): "Nevertheless, if sinus thrombosis as a puzzling and often unsuspected complication of disease is kept constantly in mind, the aetiology of certain instances of 'encephalitis', spontaneous subarachnoid haemorrhage, cerebral palsy, cortical atrophy, mental defectiveness, epilepsy and hydrocephalus may then become apparent."

## SUMMARY

(1) The characteristic features of Acute Infantile Cerebral Diplegia were illustrated by clinico-pathological reports on three cases. The disease typically affects infants and young children who are suffering from fever with dehydration or suppuration in the head or neck. The onset is sometimes, but not always, ushered in by convulsions, which may be bilateral or unilateral. Coma may ensue. On recovery, the patient is di-, tri-, or quadraplegic and may show other manifestations of cerebral degeneration, such as blindness, aphasia or dementia. The chronic phase may persist for many years until death ensues from intercurrent infection.

The distinction from Little's Disease, i.e. Congenital Cerebral Diplegia, in which the disability is noticed at or soon after birth, was emphasized.

(2) The changes in the brains from the cases studied were remarkably uniform and consisted of a diffuse sclerosis of the white matter of the dorsal parts of both cerebral hemispheres, with less extensive laminar sclerosis or ulegyria of the cortex. Softening was not seen in the cortex or white matter and the demyelination shown by the latter was less marked than the sclerosis.

It was considered that the changes in the white matter were typical of the sequelae of oedema and that the cortical degeneration was due to an accompanying, but less widespread, anoxia, such as is seen in cerebral venous thrombosis. In view of the topography of the changes, it was considered that their most probable cause was a thrombosis of the superior longitudinal sinus. The clinical histories of the reported cases were shown to be consistent with this concept.

## ACKNOWLEDGMENTS

Cases 1 and 4 were studied in the Department of Neuropathology of the Institute of Psychiatry, London and Case 3 in the Department of Pathological Anatomy of the Institut Bunge, Antwerp. It is a great pleasure to acknowledge the constant stimulating interest shown by Professor Alfred Meyer and Dr. Ludo van Bogaert during the investigation of these cases. I also wish to express my gratitude to Professor W. Scholz for his generosity in allowing me to publish Case 2 and to Drs. Mildred Creak and M. K. Beattie for enabling me to study the brain from Case 1 and to Dr. Herbert Levy in respect of Case 4. Finally, I wish to thank Dr. Martin Bodian for allowing me to refer to the cases from The Hospital for Sick Children, Great Ormond Street, studied during the tenure of the Hydrocephalus Research Fellowship at this Hospital.

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# PSYCHOSES OF CHILDBEARING*

By

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## INTRODUCTORY

It is natural to assume that because a psychosis occurs during the process of childbearing the two events are therefore necessarily associated, but the evidence is conflicting and the relationship between them has not been established with certainty. In fact no immediate dramatic cause has yet been demonstrated that would account for such mental breakdowns, and it would be surprising if it had, for the great majority of psychoses not related to maternity show no simple sequence of cause and effect.

Yet it would be wrong to dismiss without further examination an occasion so important in the life of the mother as childbirth as of no aetiological consequence. In the types of psychosis under consideration the clinical onset had often been a sudden and disturbing event, just at that particular time in the patient's life when she was confronted with the responsibility of motherhood. Further examination of the patient's history however often revealed previous evidence of emotional disturbance, or of instability in other members of her family.

Undue preoccupation with the physical complications of pregnancy and the puerperium can therefore never supply a complete answer to the problem of aetiology, more especially today when the incidence of maternal morbidity is diminishing. In this connection there is evidence of a reduction in the incidence of psychoses complicating childbirth. Thus Herzer (1906) at the beginning of the century gave an incidence rate of one in four hundred births whilst in the county of Warwickshire during the years 1948–52 the incidence was one in six hundred and eighty births. It may well be that the lower incidence is associated with the decline in maternal morbidity, and it becomes more than ever necessary to look for factors other than those associated with the obstetrical complications of childbearing, important though these may once have been.

With this in mind the whole background of the patient's personality, and that of other members of her family, has been taken into account as well as events related to the childbirth itself. No attempt has been made to describe the clinical features in detail or to classify the types of illness, the object having been to discover the broad aetiological features of psychoses of childbirth, without reference to types.

## REVIEW OF THE LITERATURE

When the literature on the subject over the last half century or so is studied it is evident that there are two main trends of opinion in regard to aetiology.

The first of these is that the pregnancy, puerperium, or lactational period are significant events in the natural history of the mental breakdown, either through physical factors such as infection, pregnancy toxaemia, haemorrhage, or hormonal disturbances, complications which are in fact already known to be associated with childbearing, or secondly from psychological causes, whether these are of an external nature such as unhappy marriage, unwanted pregnancy, recent stress, or due to unconscious psychological difficulties in the woman's adjustment to motherhood.

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Thus Galant (1927) found evidence of toxaemia, infection and physical exhaustion. Fürstner (1875) though attaching little importance to difficult labour as such, found that febrile conditions were common. Lévy-Valensi (1929) thought that anaemia, undernourishment, and exhaustion either through difficult labour or following prolonged lactation were important features, whilst Fellner (1903) and Engelhardt (1912) regarded eclampsia as an important factor. Skottowe (1942) discovered physical complications in over half his cases, e.g. pyrexia, albuminuria, pelvic thrombosis, or severe haemorrhage. Such pathological features as infection, severe haemorrhage or pregnancy toxaemia were described by Linn (1941), and Coates (1934) believed that it would eventually be shown that all cases of puerperal psychosis were of toxic origin. Bourne (1924) also stressed the importance of physical complications, though all his cases were from a maternity hospital, where difficult midwifery cases would tend to be more numerous.

In considering psychological factors Cohen (1943) drew attention to the importance of superstitions about the concept of birth itself, erroneous ideas arising from faulty sex instruction, the fear of death at the approaching labour, or concern lest the baby should be marked. Wick (1941), Saunders (1924), Boyd (1941) and also Armstrong-Jones (1923) thought that emotional distress was an important element, e.g. illegitimacy, financial worry, a feeling of inability to care for the baby, or a difficult domestic situation. Tylden (1950) has also shown how emotional factors can influence pregnancy even in normal women, and in this connection too Ellery (1927) regards a normal confinement as a source of much mental stress. Psychoanalytical methods of investigation have tended to show that a woman breaks down during childbearing because of emotional disturbances arising in her own early mental development (Jones, 1942), or because of unresolved difficulties in sexual adjustment (Zilboorg, 1931). Glover (1950) considers that normal childbearing represents the successful overcoming of an unconscious conflict. Fenichel (1946) interpreted hallucinatory states occurring after childbirth as easily recognizable wish-fulfilments. Deutsch (1947) has written of the intimate relationship between pregnancy and the woman's whole phantasy life and describes how "in pregnancy a normally performed phenomenon becomes the immediate expression of definite psychotic events".

As regards endocrine disturbances Davidson (1936) found post-mortem evidence of ovarian change. Wilson and Christie (1925) reported clinical improvement following hypodermic injections of ovarian extract, whereas Nürnberger (1936) found that patients were helped by treatment with pituitary hormone. Abély, Sizaret and Laine (1947) also thought that changes in pituitary activity were important.

The second main trend of opinion is that the pregnancy or puerperium have little or nothing to do with the mental illness, or at most act as mere precipitating events against a background of personality predisposition to psychosis, the psychosis being non-specific and indistinguishable from any other psychosis not attributable to pregnancy (Schroeder, 1942). Likewise Ordway and McIntire (1942) did not think that pregnancy was a true aetiological factor, and Aschaffenberg (1901) concluded that the puerperium was a precipitating cause only and not the fundamental one.

Childbirth itself was also deemed not to be a significant factor by Strecker and Ebaugh (1926). It is important to remember too that women may experience prolonged and difficult labour, or develop severe infection or haemorrhage, without becoming mentally ill (Frumkes, 1939). Consequently it is not surprising that the concept of predisposition has been advanced to explain why one woman and not another will develop a psychosis during childbirth. Thus Herzer (1906) found that 81 per cent. of his schizophrenic patients and 55 per cent. of his patients with manic depressive illness gave evidence of hereditary factors.

Cruickshank (1940) found a family history of epilepsy, alcoholism, psychosis or neurosis in 32 per cent. of his patients. Smalldon (1940) discovered a 25 per cent. greater inheritance of morbidity in those suffering from affective psychosis than in his schizophrenic patients, and at least a 50 per cent. greater morbid inheritance when compared with his toxic-infective group. On the other hand Solomons (1931) stated that "a careful enquiry into cases met by the writer in hospital and private practice failed invariably to elicit any hereditary factor".

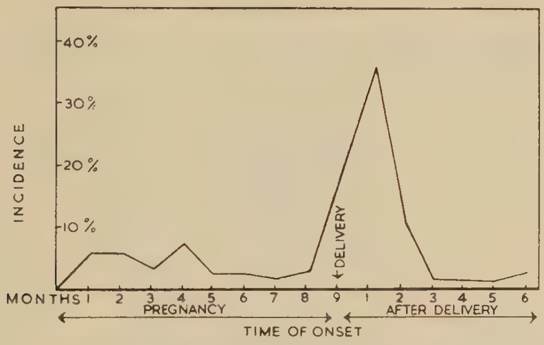

FIG. 1.—Graph showing the peak incidence of psychotic illness that occurs in the first four weeks after childbirth.

It is difficult to reconcile the view that pregnancy is without much significance with the fact that the onset of symptoms occurs with a peak incidence in the four weeks immediately after delivery. If the childbirth itself were of no import one would not expect a peak incidence of this kind to occur. This tendency for the majority of cases to occur closely together at this period is illustrated in Figure 1. The graph is drawn from a survey of all pregnancy and puerperal mental breakdowns admitted to the Central Hospital, Warwick, during a five-year period from 1944–1948. In as many as 35 per cent. of the cases the clinical onset occurred during the first four weeks after the confinement, nearly half of these becoming ill during the first week of the puerperium.

In addition to these two main views concerning aetiology, a third hypothesis suggests itself, i.e. that obstetrical complications are not a factor, but that a personality predisposition to mental disorder exists, this defect of personality relating specifically to the sexual and reproductive life of the patient.

## METHOD

Using the chi squared test, a statistical investigation has been made of sixty-seven consecutive admissions to the Central Hospital, Warwick, of psychoses complicating childbirth, whether the illness occurred during pregnancy or within six months following birth. The investigation extended over a period of thirty-one months from 1947 to 1950.

The normal controls consisted of fifty mentally normal puerperal women who had been confined in the maternity wards at St. Mary's Hospital near Rugby during the same period.

A further control series was also included, consisting of fifty consecutive admissions to the Central Hospital, of married women of a comparable age group whose psychosis was not temporally related to childbearing, and who had not previously suffered from such an illness. All the cases were examined personally and a full psychiatric social history was taken of all the psychotic patients by the Psychiatric Social Worker in interviews with the relatives.

The family history extended to the parents, siblings, aunts, uncles and grandparents. "Psychosis" included only those who had been admitted to a mental hospital and who had suffered from obvious delusional symptoms, hallucinatory experiences, gross affective disturbances, or confusion, whether related to disease or age. Suicides were also included in this group. The term "neurosis" included those members of the family who had been attended by their own

TABLE I

*Aetiological Factors as Shown by Comparison of Patients Suffering from Psychoses Associated with Childbearing with Normal Controls*

| Factor | Psychoses of Childbearing Total=67 | | Normal Puerperal Controls Total=50 | | $\chi^2$ | P |
|---|---|---|---|---|---|---|
| | No. | Per cent. | No. | Per cent. | | |
| | | Family History | | | | |
| Psychosis .. .. .. .. | 19 | 28 | 3 | 6 | 9·3 | < *·01* |
| Neurosis .. .. .. .. | 17 | 25 | 2 | 4 | 9·6 | < *·01* |
| Minor Neurotic Symptoms .. | 16 | 26 | 1 | 2 | 21·7 | < *·01* |
| Total .. .. .. | 52 | 79 | 6 | 12 | 29·2 | < *·01* |
| Epilepsy .. .. .. .. | 3 | 4 | 2 | 4 | 0·02 | 0·9 |
| Psychosomatic illness .. .. | 8 | 13 | 12 | 24 | 2·8 | 0·1 |
| | | Personal History | | | | |
| Previous history of: | | | | | | |
| Psychosis .. .. .. | 10 | 15 | — | | | |
| Neurosis .. .. .. .. | 24 | 35 | 5 | 10 | | |
| Total .. .. .. | 34 | 50 | 5 | 10 | 21·3 | < *·01* |
| Neurotic traits in childhood .. | 43 | 64 | 25 | 50 | 2·36 | 0·1 |
| Abnormal personality .. .. | 51 | 77 | 10 | 20 | 36·2 | *0·01* |
| | | Obstetrical Complications | | | | |
| Dystocia .. .. .. .. | 7 | 10 | 5 | 10 | ·16 | ·7 |
| Toxaemia of pregnancy .. .. | 5 | 7·5 | 2 | 4 | ·15 | ·7 |
| Infection .. .. .. .. | 5 | 7·5 | 4 | 8 | ·05 | ·8 |
| Severe haemorrhage .. .. | — | — | 2 | 4 | | |
| Total .. .. .. | 17 | 25 | 13 | 26 | ·0046 | ·95 |

The italicized values of P are "significant" taking the conventional level of significance when P=0·05.

doctor for an illness resulting in absence from work for many weeks or months, the symptoms of which conformed to those associated with the accepted clinical varieties of neurosis, namely, hysteria, anxiety states, neurotic depression, or obsessional neurosis. Under "minor neurotic symptoms" were included stammering, nervousness, blushing, frequent unexplained headaches, undue irritability, and mild dyspepsia. Included under "psychosomatic disorders" were peptic ulcer, ulcerative colitis, asthma, rheumatoid arthritis, migraine, and recurrent attacks of eczema. A history of epilepsy was dealt with as a separate factor.

The same criteria were used in investigating the personal psychiatric history of the patient. Two further categories were included here, namely a history of neurotic traits in childhood, and a history of abnormal personality. Neurotic childhood traits consisted in nail biting, enuresis, excessive fear of the dark, undue nervousness, blushing, shyness, night terrors, sleep walking, temper tantrums, and stammering. Abnormal personality was less easy to define, but the criteria laid down by Slater (1943) were adopted, i.e. hysterical personality, anxious personality, unstable mood, obsessional personality, hypochondriacal personality, paranoid sensitive personality, unsociable personality, and anergic personality.

## RESULTS

*Comparison with normal controls.* Taking a conventional level of significance when P=0·05, there was found to be more than a chance association between a family history of psychosis, neurosis and minor neurotic symptoms on the one hand and mental disorder of childbearing on the other. There was no significant association with epilepsy or with psychosomatic disorders.

There was also an association between a personal history of psychosis, neurosis or of abnormality of personality and the development later of a mental illness associated with childbearing. There was no correlation with a history of childhood neurotic traits.

TABLE II

*Comparison of Aetiological Factors in Psychoses Associated with Childbearing and Psychoses Not so Associated but Occurring in Women of a Comparable Age Group*

| Factor | Psychoses Associated with Childbearing | | Psychoses Not Associated with Childbearing | | | |
|---|---|---|---|---|---|---|
| | No. | Per cent. | No. | Per cent. | Statistical Comparison with Normal Controls $\chi^2$ | P |
| Average age .. .. .. | 30·4 years | | 35·2 years | | | |
| Family history: | | | | | | |
| Psychosis .. .. .. | 19 | 28 | 10 | 20 | 4·3 | *·04* |
| Neurosis .. .. .. .. | 17 | 25 | 10 | 20 | 6·1 | *·02* |
| Minor neurotic symptoms .. | 16 | 26 | 13 | 26 | 12·0 | *·01* |
| Epilepsy .. .. .. .. | 3 | 4 | 2 | 4 | ·02 | ·9 |
| Psychosomatic illness .. .. | 8 | 13 | 11 | 22 | ·056 | ·98 |
| Personal history: | | | | | | |
| Neurosis .. .. .. .. | 24 | 35 | 15 | 30 | 6·2 | *·02* |
| Psychosis .. .. .. | 10 | 15 | 11 | 22 | 12·0 | < *·01* |
| Neurotic traits in childhood .. | 43 | 64 | 41 | 82 | 11·6 | <*0·01* |
| Abnormal personality .. .. | 51 | 77 | 34 | 68 | 23·4 | <*0·01* |

The italicized values of P are "significant" taking the conventional level of significance when P=0·05.

From these figures it is therefore concluded that a personality predisposition exists, as shown by the personal history, and also an hereditary predisposition as shown by the high incidence of abnormality in the family history.

*Obstetrical complications.* Do obstetrical complications show any correlation with psychosis developing at this period of a woman's life? As already recounted, previous workers have often been convinced of an essential relationship between the two, and indeed this is frequently taught even today. However, under modern conditions of obstetric practice the results displayed in Table I demonstrate that there is no statistical association. Neither is a psychosis more likely to occur in relation to a first pregnancy, with its greater incidence of complications, as is illustrated in Table III. In this table it is also shown that the age of the patient makes no difference to her liability to develop mental illness as a complication of childbirth.

TABLE III

*Distribution in Relation to Age and Parity*

| | Psychoses Associated with Childbearing | | Normal Controls | | | |
|---|---|---|---|---|---|---|
| | No. | Per cent. | No. | Per cent. | $\chi^2$ | P |
| Age Groups: | | | | | | |
| 15–20 years .. .. .. | 3 | 4·5 | 2 | 4 | ·11 | 0·7 |
| 20–25 ,, .. .. .. | 12 | 18 | 16 | 32 | 2·02 | ·1 |
| 25–30 ,, .. .. .. | 15 | 22 | 10 | 20 | ·84 | ·4 |
| 30–35 ,, .. .. .. | 22 | 35 | 14 | 28 | ·13 | ·7 |
| 35–40 ,, .. .. .. | 11 | 16 | 7 | 14 | ·018 | ·9 |
| 40–45 ,, .. .. .. | 4 | 6 | 1 | 2 | ·35 | ·6 |
| Total .. .. .. | 67 | | 50 | | | |
| Parity: | | | | | | |
| Para 1 .. .. .. | 31 | 46 | 22 | 44 | ·004 | ·9 |
| 2 .. .. .. | 17 | 26 | 15 | 30 | ·12 | ·7 |
| 3 .. .. .. | 8 | 12 | 8 | 16 | ·13 | ·7 |
| 4 .. .. .. | 9 | 13 | 3 | 6 | 1·0 | ·3 |
| 5 .. .. .. | 2 | 3 | 2 | 4 | ·045 | ·8 |
| Total .. .. .. | 67 | | 50 | | | |

Some authors have sought to explain puerperal and pregnancy psychoses as resulting from genito-urinary infection, which clinically may have gone unrecognized. Baruk (1938) stated that *B. Coli* infection of the urinary tract could be found in nearly all cases of puerperal psychosis. Toulouse, Marchand and Courtois (1930) described post-mortem evidence of renal suppuration, and Parfitt (1934) found albuminuria in thirteen out of fourteen cases of mental illness complicating pregnancy and the puerperium. A catheter specimen of urine obtained under strict aseptic precautions from seventeen consecutive cases failed to confirm any of these findings (Table IV). Only one patient showed evidence of urinary infection, and this was already known because of clinical symptoms. Apart from this one case, none of these patients had albuminuria.

The E.S.R. was estimated in twenty consecutive cases, using the Wintrobe method (Whitby and Britton, 1942) and taking the normal range in

TABLE IV

*Analysis of Catheter Specimens of Urine*

| Case No. | Period of Pregnancy or Puerperium | Albumin | Centrifuged Deposit: Epithelial Cells | R.B.C.s | Leucocytes | Organisms | Evidence of Urinary Infection |
|---|---|---|---|---|---|---|---|
| 51 | 12 weeks following delivery .. | — | — | + | — | — | Nil |
| 52 | 8 weeks following delivery .. | — | — | — | — | — | Nil |
| 53 | | | | | | Too resistive | |
| 54 | 2 weeks following delivery .. | — | — | — | — | — | Nil |
| 55 | 3 days following delivery .. | 40 mg. per cent. | — | — | ++ | ++ (Gram-VE) | Yes |
| 56 | | | | | | Too resistive | |
| 57 | 2 weeks following delivery .. | — | — | — | — | — | Nil |
| 58 | 4 weeks following delivery .. | — | + | — | — | — | Nil |
| 59 | 3 weeks following delivery .. | — | — | — | — | — | Nil |
| 60 | 20 weeks following delivery .. | — | + | — | — | — | Nil |
| 61 | 20 weeks pregnant .. .. | — | + | — | — | — | Nil |
| 62 | 16 weeks pregnant .. .. | — | ++ | — | — | — | Nil |
| 63 | 2 weeks following delivery .. | — | + | — | — | — | Nil |
| 64 | 4 weeks following delivery .. | — | + | — | — | — | Nil |
| 65 | 3 weeks following delivery .. | — | + | — | — | — | Nil |
| 66 | | | | | | Too resistive | |
| 67 | 1 week following delivery .. | — | + | — | — | — | Nil |

TABLE V

*Showing Results of Examination of the Erythrocyte Sedimentation Rate*

| Case No. | Period of Pregnancy or Puerperium | E.S.R. (Wintrobe) (Fall in one hour) | Corrected E.S.R. | Clinical Evidence of Infection |
|---|---|---|---|---|
| 48 | 3rd month of pregnancy | 18 m | 10 m | Nil |
| 49 | | Refused investigation | | |
| 50 | 5th month of pregnancy | 8 m | 3 m | Nil |
| 51 | 3rd month after delivery | 16 m | 8 m | Nil |
| 52 | 2nd month after delivery | 17 m | 17 m | Nil |
| 53 | | Specimen clotted | | |
| 54 | 2 weeks after delivery | 12 m | 12 m | Nil |
| 55 | | Restless patient | | |
| 56 | | Restless patient | | |
| 57 | 2 weeks after delivery | 3 m | 3 m | Nil |
| 58 | 1 month after delivery | 8 m | 8 m | Nil |
| 59 | 3 weeks after delivery | 46 m | 40 m | Retained products of conception. Pyrexial |
| 60 | 5 months after delivery | 20 m | 20 m | Nil |
| 61 | 5th month of pregnancy | 15 m | 11 m | Nil |
| 62 | 4th month of pregnancy | 48 m | 41 m | Nil |
| 63 | 2 weeks after delivery | 39 m | 39 m | Nil |
| 64 | 4 weeks after delivery | 13 m | 10 m | Nil |
| 65 | 3 weeks after delivery | 51 m | 34 m | Retained Placenta |
| 66 | | Resistive patient | | |
| 67 | 1 week after delivery | 54 m | 26 m | Nil |

women to be 0–20 mm. fall in one hour. Table V shows that five patients had an abnormally high E.S.R., but two of these already showed clinical evidence of infection. Thus only three of the twenty patients might have had a low grade infection that had been unrecognized, but according to Nichols (1942) even in normal pregnancy the E.S.R. is often raised, reaching a peak at about parturition.

There was thus no clear general evidence that hidden systemic infection could have been an aetiological factor.

Further evidence that complications of pregnancy and the puerperium are not a factor is shown by the fact that during the same period over which these cases were collected, six childless women who had adopted an infant were under treatment at the same hospital with a depressive psychosis, not unlike the cases of puerperal psychosis in symptomatology, the symptoms having occurred within a few weeks of the adoption. It is tempting therefore to think that it is the psychological impact of the child which is the disturbing factor, and not the physical act of birth.

*Comparison with psychoses not associated with childbearing.* Having drawn attention to the aetiological background against which a puerperal or pregnancy psychosis might supervene, is there any evidence to show from the factors studied that this background is in any way different from that associated with psychoses which bear no relationship to childbearing? An examination of Table II which shows a comparison with fifty such controls, who were married women of a comparable age group, illustrates that the aetiological background is similar in the two series.

## DISCUSSION

From the similarities that have been observed with other types of mental disorder, it is evident that personality predisposition exists in both, and if this is so the childbirth itself and the complications arising from it assume less significance aetiologically, just as with other types of psychosis immediate events are not often the true cause of the illness. The lack of statistical relationship with obstetrical complications bears this out. But it remains unexplained why these women should have broken down during childbirth, though the psychotic controls, most of whom were mothers, survived this only to become ill in other circumstances. Having drawn attention to similarities with other types of psychosis, it is then perhaps more important to see whether differences exist, though these may not have been apparent in the statistical analysis so far. I am of the opinion that differences do exist, and that these differences point to the fact that the defect of personality in these women lies in the reproductive function, particularly where this has related to the setting up of a home and the rearing of children in the normal fashion. The same differences are noted also when comparison is made with the normal controls.

Thus there is a strikingly high proportion of single women in the series, namely, seven out of sixty-seven, or approximately 10 per cent., whereas only one of the psychotic controls and none of the normal controls had given birth to a child before marriage. Nor was this social inadequacy due to intellectual limitations, for of the six single women, four were of normal intelligence, one of superior intelligence and only one mentally dull.

A further five had become pregnant as a result of extra-marital relationships, whereas this had occurred in none of the psychotic controls. Thus an illicit pregnancy had befallen twelve out of the sixty-seven patients or 18·5 per cent., a statistically significant proportion, for even when former pregnancies were taken into account only one of the normal controls and one of the psychotic controls had so conceived ($P = < 0 \cdot 01$). This is not to be confused with unwanted pregnancy; nine of the normal controls admitted to this, but had nevertheless become successful mothers.

The question of emotional stress arises here and cannot be altogether separated out as a contributory aetiological factor. As many as 34 per cent. of the series admitted experiencing emotional stress, but so also did 30 per cent. of the psychotic controls. Moreover the single women seemed to have accepted the pregnancy without much show of conscious emotional disturbance. What is even more impressive is that one of these had had a child before, and three of them subsequently gave birth to a second illegitimate child.

Three of the pregnancies had been the result of an incestuous union, perhaps expressing instability of reproductive function not only in the patient but in other members of the family also. A further four of the series had been sexually promiscuous, whereas none of the normal or psychotic controls had been so.

The abnormalities of reproductive life, especially in its social aspect, though not universally applicable to the whole series of childbearing psychoses, are nevertheless striking enough to arouse suspicion that a psychosis supervening upon pregnancy is not an isolated and inexplicable event, but is expressive of a deep-seated disorder or maladjustment of the reproductive function.

Another factor which illustrates this disturbance of reproductive function in these women is the embarrassed mother–child relationship. What complex emotional difficulties have to be surmounted even in the most normal of pregnancies, especially where the mother's relationship to her new-born child is concerned, have been described by Morris (1950). But in the mothers studied here there seemed to have been no constructive effort to overcome these difficulties in the days and weeks following birth, sometimes even before the psychosis developed. In the women who suffered from an affective psychosis, who comprised 60 per cent. of the total, there was in every case an abnormal emotional relationship to the child, expressing itself as a perverted hatred, indifference, or phobia that the child would be injured or killed, or even a denial that the child was theirs. This distorted relationship was found in some of the patients to persist or recur at intervals for some years after the psychosis had subsided. I have found this same symptom to occur in women who had not suffered from a psychosis during childbearing, but closer enquiry has always revealed that there had been a period of depression during the puerperium, combined with an awareness of difficulty in securing a good emotional relationship with the child.

One patient had a constant phobia that her boy would fall down the stairs and be killed. Another had a haunting fear that her mother would drop the child, causing its death. In two of the cases the mother had an obsessional preoccupation that she would injure her own child. Both looked after their children with scrupulous care, yet both had homicidal phantasies about them. One had frequent troubling dreams in which she murdered her child, whilst another repeatedly dreamt that there was nobody to care for the child, which died of starvation. Some of the patients felt they could no longer be responsible for the infant, and one was seriously considering having the child adopted. Another had a feeling that the baby was not hers, saying "I cannot realize the baby is mine. I cannot think it came from my body." The depersonalization she was experiencing extended to her state of awareness of her own child. The idea persisted for three years after she had been discharged from hospital. Yet another had a delusion that she had "no mother instinct".

The puerperal schizophrenics did not show such specific relationships, but the mother on the whole tended to deny the existence of the child. That such a relationship may have been fundamental was however shown by one patient who had a delusion that her child had been offered as a religious sacrifice.

Victorhoff (1952) in his series of cases did not think that this perverted attitude was a desire to kill the child, but rather was evidence that the patient valued herself as an ineffective mother.

Such evidence of maladjustment to marriage as these patients have shown, together with this perverted attitude towards the child seems to indicate a lack of what Bowlby (1953) has called the normal instinctive and emotional equipment to set up a home and rear children. There has in fact been a breakdown of motherhood, the childbirth itself having been the means whereby the defect of personality became manifest, rather than a cause of the mental illness. The fact that there is a family history of mental instability in a significant proportion of these cases makes it likely that the defect of personality may be of an hereditary nature.

## Conclusions

Patients suffering from psychoses complicating pregnancy and childbirth have a statistically greater incidence of previous mental instability than do normal puerperal controls, and a more unstable family history.

It is suggested that there is a defect of personality particularly where this concerns reproductive function.

Obstetrical complications are not a cause of puerperal and pregnancy psychoses.

Cases of puerperal affective psychoses show a specific feature, namely, a perverted emotional relationship towards the child.

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# THE CLINICAL RESPONSE OF PSYCHONEUROTICS TO CHLORPROMAZINE

By

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Chlorpromazine hydrochloride (3-chloro-10 (3'-dimethylamino-propyl)-phenothiazine) or "largactil" is being widely tried out as a form of therapy in psychiatric disorders. Papers have appeared describing its use in comparatively severe conditions encountered in in-patient mental hospital practice (e.g. Anton-Stephens, 1954) and in psychoneurotics (e.g. Garmany, May and Folkson, 1954). In the psychoneurotic group in particular, the drug is reported to be helpful in reducing tension and diminishing pre-occupation with worries, fears, and concomitant symptoms. These two properties—the reduction of tension and the production of a feeling of relative indifference to distressing stimuli—were amongst those originally attributed to chlorpromazine by Sigwald and Bouttier (1953) and, of course, they approximate to the characteristic changes resulting from prefrontal leucotomy (Partridge, 1950). The effects of this operative procedure have been extensively studied in relationship to such factors as the previous personality of the patient and the duration of the illness involved (e.g. Baker and Minski, 1951) and it was considered that it might be of value to investigate similar factors in patients treated with chlorpromazine. It is true that prefrontal leucotomy entails structural damage as a result of which the previous personality, for example, may be expected to have a significant bearing on the therapeutic outcome, but even with patients treated by chlorpromazine the ultimate result may depend, at least to some extent, on the inherent make-up of the individual or the symptom-complex from which he is suffering. It was in order to study the relationship between factors of this nature and chlorpromazine treatment that the following investigation was undertaken.

## Material and Methods

The fifty patients included in this report were treated in out-patient departments of general hospitals. All were suffering from psychoneurotic disorders, their clinical conditions, age, and sex being summarized in Tables I, II, and III

Table I

*Diagnosis and Clinical Response*

| | | | Obsessional State | | | |
|---|---|---|---|---|---|---|
| Diagnosis | Anxiety State | Hysterical Reaction | Mainly Ruminative | Mainly Compulsive | Neurotic Depression | Total |
| Remission .. | 8 | 2 | — | — | 1 | 11 |
| Improved .. | 10 | 8 | 2 | 1 | 1 | 22 |
| Unchanged .. | 2 | 10 | 1 | — | 4 | 17 |
| Number .. | 20 | 20 | 3 | 1 | 6 | 50 |

TABLE II

*Age Group and Clinical Response*

| Age Range in Years | 11–20 | 21–30 | 31–40 | 41–50 | 51–60 | 61–70 | 71–80 |
|---|---|---|---|---|---|---|---|
| Remission .. .. | — | 4 | 4 | — | 2 | 1 | — |
| Improved .. .. | — | 8 | 7 | 3 | 3 | — | 1 |
| Unchanged .. | — | 2 | 2 | 4 | 7 | 1 | 1 |

TABLE III

*Sex Distribution and Clinical Response*

| | Males | Females |
|---|---|---|
| Remission .. .. | 2 | 9 |
| Improved .. .. | 8 | 14 |
| Unchanged .. .. | 9 | 8 |

respectively. In addition, an assessment was made of the presence or absence of overt neurotic traits in the previous personality, and the duration of the current illness, prior to commencing chlorpromazine treatment, was also computed (Tables IV and V respectively).

TABLE IV

*Previous Personality and Clinical Response*

| Previous Personality | Overt Neurotic Traits Present | Overt Neurotic Traits Absent |
|---|---|---|
| Remission .. .. .. .. | 5 | 6 |
| Improved .. .. .. .. | 16 | 6 |
| Unchanged .. .. .. .. | 10 | 7 |

TABLE V

*Duration of Illness and Clinical Response*

| Duration of Illness | Less than 1 Year | 1–3 Years | Over 3 Years |
|---|---|---|---|
| Remission .. .. .. | 4 | 3 | 4 |
| Improved .. .. .. | 6 | 9 | 7 |
| Unchanged .. .. | 2 | 6 | 9 |

In view of the fact that the subjects were out-patients, administration of chlorpromazine was limited to the oral route. The initial dose in each case was 25 mg. t.d.s. the patients being asked to lie supine for 30 minutes, after taking the drug in order to avoid side-effects. Depending on the response of the patients, the dosage of the drug was subsequently raised in many cases, the maximum dose given being 75 mg. t.d.s. The majority of patients, however, received only 25 to 50 mg. t.d.s.

All the patients included in this study were kept on chlorpromazine medication for three months. At the end of this period an assessment was made of the clinical response on the basis of the following three broad groupings (Table I):

1. *Complete Remission.* This, of course, applied to those cases which became symptom-free. Case No. 34 may be taken as an example. Patient was a 40-year-old woman with overt anxiety symptoms for the previous five years. There was marked fear of crowds, pre-occupation with physical disease, and specific phobic ideas concerning cancer. Tension, irritability, and tiredness were in evidence. Following chlorpromazine medication (25 mg. t.d.s.) she became placid, composed and cheerful. She no longer mentioned any phobic symptoms. When asked about her fears, she smiled and readily stated that they had ceased to worry her. She was running the home without difficulty for her husband and young son and coping quite satisfactorily with her normal household chores.

2. *Improved.* This assessment referred to cases in which some clinical alleviation of symptoms was obvious to the patients and the writer. This category can be illustrated by Case No. 29. The patient was a 31-year-old married man with a history of severe obsessive–compulsive symptoms, and marked fears of fainting, for the previous twelve months. He had always been of typical obsessional make-up. His presenting symptoms were precipitated by promotion to the position of foreman and consisted of excessive checking and re-checking of work done in the factory with resultant difficulty in coping with his responsibilities. Subjective tension complained of but not obvious at interview. Placed on chlorpromazine (25 mg. t.d.s.). Fear of fainting subsided and there was a marked decrease in compulsive symptoms. It remained evident, of course, that he still had his obsessional tendencies but these had receded so much into the background that they did not materially interfere with his ability to carry on with his normal work.

3. *Unchanged.* This group included those cases in which there was no obvious improvement in the presenting symptoms.

## RESULTS

More than three-fifths of the cases gained material benefit from chlorpromazine treatment. Approximately one-fifth became completely symptom-free. Anxiety states showed the most favourable response to treatment, especially in relationship to complete remission of symptoms. Taking the categories of "remission" and "improved" together, application of the exact $\chi^2$ test showed that the difference between the response of anxiety states and the other diagnostic categories was significant (P=0·0035).

Those cases under 40 appeared to respond better than the older age groups. By combining the "remission" and "improved" categories, this difference was shown to be significant (Difference/S.E.=41·7/13·4).

Table III suggests that females fared better than males, but on the comparatively small number of patients studied, the figures were not significant. ("Remission" and "improved" taken together: difference/S.E.=21·6/13·8.)

The previous personality did not appear to exert any significant effect on the therapeutic outcome. (Combination of "remission" and "improved" categories: difference/S.E.=4·5/13·8.)

The duration of the illness involved was not shown to have any material influence on the chances of remission or improvement. ("Remission" and "improved" taken together: $\chi^2$=2·71.)

## COMMENT

In this series, patients suffering from anxiety states showed a significantly better response to treatment than those in the other diagnostic categories. This is in line with the finding of Garmany, May and Folkson (1954), that the best results are obtained in cases in which tension is the most conspicuous feature. They stated, however, that patients with predominantly obsessional symptomatology did badly, though their clinical summaries of cases with obsessional features showed some relief of tension in all the patients concerned. In view of the latter, one would have expected that their cases would have shown a somewhat better response to treatment, especially taking into account the fact that prefrontal leucotomy, largely as a result of reducing tension, is frequently successful in obsessional states. In the present study, though the numbers are small, three out of the four patients with obsessional states showed a material degree of improvement. With the relief of associated tension, the obsessional tendencies became correspondingly less troublesome and in one case they virtually disappeared. These observations lend some support to the views of Sigwald and Bouttier (1953b) and Winkelman (1954), concerning the beneficial effects of chlorpromazine in obsessional conditions. In fact, Winkelman states that no obsessional patient should undergo prefrontal leucotomy until chlorpromazine has been given a trial. A somewhat similar opinion has been expressed elsewhere. (Leading Article, *British Medical Journal*, 1954, **2**, 581.)

When depressive or hysterical features predominated in the symptom-complex, the results were not good, these findings being similar to those of Garmany *et al.* (1954).

As with prefrontal leucotomy (Baker and Minski, 1951; Gillies, Hickson and Mayer-Gross, 1952), there is a suggestion that females respond better than males, but the relevant figures in this series are not significant. Unlike the results of leucotomy (*ibid.*), younger patients fared better than those in the older age groups.

The presence of neurotic traits in the previous personality, and the duration of the illness involved, were not shown to be significant factors in the short-term response to treatment.

## SUMMARY

Fifty psychoneurotics were treated on an out-patient basis for 3 months with oral doses of chlorpromazine ranging from 25 mg. t.d.s. to 75 mg. t.d.s.

Approximately three-fifths of the cases gained substantial benefit from treatment.

Anxiety states showed a statistically significant better response than the other diagnostic groups. This supports the view that the main effect of the drug is in the relief of tension. Some obsessional states showed material improvement. Hysterical and depressive reactions did not respond well.

Patients in the first four decades fared better than the older age groups.

There was no evidence that the previous personality, or the duration of the illness involved, were significant factors influencing the clinical response.

The findings, especially in relationship to prefrontal leucotomy, are briefly commented upon.

## ACKNOWLEDGMENTS

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# A BEHAVIOURAL RATING SCALE FOR MENTAL PATIENTS

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In connection with a demonstration programme of comprehensive psychiatric care for hospitalized schizophrenic patients, it was necessary to develop a rapid and effective method for rating patients' ward adjustment and social behaviour. The scale, entitled the Albany Behavioural Rating Scale (ABRS), and its validation, are described in this report. The nature of the problem required that the scale be readable, easily completed and scored, and suitable for use by nursing and rehabilitation personnel (OT, CT, Music Therapist, etc.). Further requirements included adequate scoring reliability and validity, as well as amenability to quantification.

Various rating scales have been described in the psychiatric literature, but these did not meet our needs. Some were too cumbersome and time-consuming. Others required individual psychiatric interview. Frequently they demanded high literacy of the rater. Certain scales are indeed useful for special purposes, as for example the MSRPP (Lorr, 1953) which can be employed with confidence as an aid to psychiatric classification. Lucero and Meyer (1951) have discussed the requirements of an adequate rating scale.

## METHOD

*Development of the Scale.* A scale was organized of items selected on the basis of clinical judgment. Materials from existing rating scales were reviewed (Lorr, 1953; Lucero and Meyer, 1951; Malamud and Sands, 1947; Wittman, 1941), and they contributed to the composition of the present scale. The majority of items were adapted from the listing of Ferguson, McReynolds, and Ballachey (1952). One hundred items were chosen; they included six major areas. Each item was presented as a statement in the affirmative with "yes" or "no" to be encircled by the rater. The complete scale is reproduced at the end of this paper.

The items for the six areas were scattered throughout the final scale. The statements subsumed under the six main headings were not mutually exclusive, and certain items might reasonably have been contained in two or more areas. This classification was the result of individual ratings of each item by three experienced clinical psychologists,* who then met in conference for joint discussion of the items and their proper placement within the classes of content.

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* Dr. Manual Aronson, whose co-operation is gratefully acknowledged, and the authors.

Area I—*Self Care:* Eighteen items pertaining to the patient's adequacy in caring for himself; his appearance, personal habits, and ability to comply with ward routine. (Nos. 2, 8, 14, 15, 20, 21, 29, 36, 42, 47, 56, 64, 71, 77, 85, 91, 98, 100.)

Area II—*Orientation:* Eight items. Does the patient know who he is, where he is; is he oriented in time? (Nos. 1, 19, 49, 51, 52, 73, 82, 97.)

Area III—*Communication and Socialization:* Twenty-eight statements pertaining to interpersonal relations with fellow patients, ward personnel, and family. Items probing communication in terms of the patient's speech, letter writing, etc. (Nos. 3, 7, 9, 10, 12, 13, 16, 18, 22, 24, 25, 31, 34, 47, 48, 55, 57, 60, 64, 66, 69, 72, 75, 78, 81, 87, 93, 96.)

Area IV—*Psychotic Behaviour:* Eighteen statements concerning the presence of psychotic manifestations such as delusions and hallucinations. (Nos. 4, 5, 6, 17, 23, 32, 39, 43, 62, 68, 76, 79, 83, 84, 86, 88, 89, 92.)

Area V—*Co-operation:* Fourteen items describing possible patient reactions ranging on a continuum from co-operative to hostile and openly assaultive behaviour. (Nos. 11, 26, 27, 30, 35, 41, 45, 50, 65, 70, 74, 89, 95, 98.)

Area VI—*Reaction to Environment:* Fourteen items which probe the patient's interest in and reactions to his environment. (Nos. 3, 9, 33, 38, 40, 44, 46, 53, 54, 58, 61, 67, 94, 99.)

*Scoring.* Total number of items was 100, with lowest possible score at 0 and highest at 100. The healthier direction of response ("yes" *or* "no") for each item was designated *a priori* according to usual clinical standards. A higher score signified healthier ward behaviour, with one point accruing for each item rated in the healthy direction. A key was utilized to minimize scoring time which then required under two minutes per scale.

*Reliability.* The patients of one active treatment ward (N=31) were rated independently on the scale by each of two nurses assigned to that ward. The raters were given no training beyond the initial instructions for the scale and the definition of any words which they did not understand. The Pearson product–moment coefficient of correlation between the two sets of ratings was +·79. Since this was an active treatment ward (EST, Chlorpromozine, ICT), the individual patients were more than ordinarily variable in their behaviour and showed frequent temporary fluctuations in their adjustment. On this account the scoring of the ABRS assumed greater difficulty than would have been the case for a continued treatment ward. The correlation coefficient of ·79 was therefore a conservative estimate of the scale's reliability. A second reliability study was made on a continued treatment ward for schizophrenic patients (N=25). These subjects were rated independently by each of two nurses assigned to that ward. No special training was given. The Pearson product–moment coefficient of correlation between the two sets of ratings was ·84. Rating reliability is satisfactory.for clinical and research purposes.

Reliability as consistency of the scale was estimated by the Richardson and Kuder method of rational equivalence (Guilford, 1950). This was calculated from the scores obtained by all patients in the two contrasted wards, 9D and 10C (N=56). The reliability coefficient thus obtained was ·97, which is high.

The standard error of an obtained score is a measure of the error made in taking an individual's obtained score as an estimate of his true score. This was calculated from the reliability coefficient reported above: the standard error was 3·2, or 3 in whole numbers. The odds are therefore 2 : 1 that the obtained score made by any individual in the group does not differ from his true score by more than ±3 points.

*Validity*. The patients on each of two wards, 10C and 9D, were rated by their respective ward nurses with the Albany Behavioural Rating Scale. Age, educational–vocational levels, and chronicity were equivalent. Ward 10C contained long-term patients who made a poor adjustment; they required closed ward supervision. In contrast, ward 9D patients—although long-term—made a satisfactory open ward adjustment requiring only minimal staff supervision; the majority were privileged patients. They were free to come and go; they attended general hospital functions. Clinically these two ward populations showed marked contrast in behaviour and in interpersonal communication. They constituted the validating criteria for the rating scale. The latter was tested for its ability to differentiate these two populations, one from the other.

A replicated experiment was conducted. All patients in each ward (N=28/ward) were rated by their respective ward nurse. The patients of each ward were then listed in ascending order according to their ABRS scores. The odd-numbered patients of each ward (9D vs 10C) were selected to constitute the first experiment (N=28). Means and standard deviations were calculated, and statistical tests of the significance of the differences between these were made (t-tests and F-tests). Results are reported in Table I. This procedure was repeated with the even-numbered patients (N=28). Comparative results are reported in Table I. Finally, the scores of the total populations of each ward were submitted to the same statistical treatment (N=56). The outcome is again reproduced in Table I. In every instance the better adjusted patients (ward 9D) attained a significantly higher mean adjustment score (P<·001) than did the more poorly adjusted patients (ward 10C). A chi square test of independence between ward adjustment and ABRS score led to rejection of the hypothesis that these two qualities were independent of each other ($\chi^2$=12·07, P<·001). They were definitely interrelated. The coefficient of contingency between these two qualities, corrected for broad categories (Guilford, 1950) was ·60. All results point to the validity of the ABRS as an indicator of ward adjustment and social communication for long-term or psychotic patients.

TABLE I

*Behavioural Rating Scale Comparative Data Ward 10C VS 9D*

| Patients | Mean | t | p | Variance | F |
|---|---|---|---|---|---|
| 10C (odd) (N=14) .. | 34·78 | | | 199·56 | |
| VS .. .. .. | | 4·24 | <·001 | | 1·30* |
| 9D (odd) (N=14) .. .. | 58·71 | | | 260·00 | |
| 10C (even) (N=14) .. | 36·57 | | | 221·90 | |
| VS .. .. .. | | 4·40 | <·001 | | 1·03* |
| 9D (even) (N=14) .. .. | 61·50 | | | 228·42 | |
| 10C Total (N=28) .. | 35·67 | | | 203·54 | |
| VS .. .. .. | | 6·22 | <·001 | | 1·12* |
| 9D Total (N=28) .. .. | 60·10 | | | 228·15 | |

* Not significant at 5 per cent. level of confidence.

Each item of the ABRS was tested individually by chi square for its ability to differentiate between the two contrasted wards. This too was done as a replication experiment. Each of the patients on 9D and 10C were ranked according to score within their respective wards. These two lists were each divided into split halves (odd–even), and the odd-numbered 10C patients were then tested against the odd-numbered 9D patients (N=28) for each ABRS

TABLE II

*Chi Square Analysis, Significant Items*

| Item No. | Even (N=28) Experiment | Odd (N=28) Experiment | Total (N=56) |
|---|---|---|---|
| 3 | ·01 | > ·30 | ·02 |
| 4 | ·05 | ·20 | ·01 |
| 5 | ·05* | > ·30 | ·02 |
| 6 | ·001 | ·01 | ·001 |
| 7 | ·05* | > ·30 | ·02* |
| 8 | > ·30 | ·01 | ·01 |
| 10 | > ·30* | ·05* | ·20 |
| 11 | ·05* | > ·30 | ·02* |
| 15 | ·10 | ·30 | ·02 |
| 16 | ·30 | ·01 | ·01 |
| 17 | ·20 | ·01 | ·001 |
| 18 | ·05* | > ·30 | ·30* |
| 20 | ·20 | ·01* | ·01 |
| 24 | ·01 | > ·30 | ·01 |
| 25 | ·20 | ·30 | ·02 |
| 26 | ·20 | ·10 | ·02 |
| 27 | > ·30 | ·02* | ·02 |
| 28 | ·20 | > ·30 | ·05 |
| 29 | ·01* | ·02* | ·001 |
| 31 | ·01 | ·05 | ·001 |
| 34 | ·30 | ·30 | ·05 |
| 35 | ·10 | ·10 | ·01 |
| 36 | ·20 | ·20 | ·02 |
| 41 | ·001 | ·001 | ·001 |
| 42 | ·10 | ·05 | ·01 |
| 44 | ·10 | ·10 | ·01 |
| 46 | ·01 | ·05 | ·001 |
| 47 | > ·30 | ·05 | ·02 |
| 54 | ·20 | ·20 | ·02 |
| 56 | ·30 | ·10 | ·02 |
| 57 | ·20 | ·10 | ·05 |
| 58 | ·20 | ·30 | ·05 |
| 60 | ·10 | ·30 | ·05 |
| 62 | ·05 | > ·30 | ·02 |
| 63 | ·01* | ·20 | ·01 |
| 64 | ·30 | ·10 | ·02 |
| 65 | ·05* | > ·30 | ·05 |
| 67 | ·01 | ·20 | ·001 |
| 72 | ·05* | > ·30 | ·02* |
| 73 | ·001 | ·05 | ·001 |
| 75 | ·01 | ·20 | ·01 |
| 77 | ·10 | ·10 | ·01 |
| 78 | ·05* | ·10 | ·01 |
| 80 | ·01* | ·10 | ·001 |
| 82 | ·001 | ·20 | ·001 |
| 84 | ·01* | ·01* | ·001 |
| 86 | ·20 | ·01 | ·01 |
| 87 | ·01* | ·10 | ·001 |
| 89 | ·30 | ·20 | ·05 |
| 90 | ·01 | ·05 | ·001 |
| 93 | ·05* | > ·30 | ·10 |
| 94 | ·20 | ·30 | ·05 |
| 96 | ·05* | > ·30 | ·20* |
| 97 | ·01 | ·20 | ·001 |
| 98 | > ·30 | ·05 | ·05 |

* Theoretical cell frequency below 5.

item by chi square tests of independence. Dichotomization point was set at the median for the twenty-eight patients. This was repeated for the even-numbered patients. Finally, chi square tests of independence were made for each item of the ABRS, utilizing the total sample (N=56). Results of the chi square tests are reported in Table II, which includes findings for each of the split halves (N=28) as well as for the total (N=56). Reported in Table II are all ABRS items which differentiated significantly at the 5 per cent. level of probability or better ($\leq \cdot 05$) in at least one of the split-half experiments or in the total. This table gives a view of the consistency of the significant individual items, from experiment to experiment. Excluded are all items which did not attain statistical significance at least once.

It will be recalled that the healthier direction for each ABRS item had been previously designated on the basis of clinical judgment. Since the actual chi square test was applied to the hypothesis that membership in ward 9D was unassociated with a *healthier* rating for each item, then the true probability level was P/2 rather than the P figure reported in Table II. The probabilities reported in Table II are therefore very conservative estimates, and the statistical significance of those items is even greater than reported.

It is apparent that some items made only minor contribution to the differentiation of patients from two criterion wards. Nevertheless, they should be retained in the ABRS. Cumulatively they may attain considerable differentiating power. Furthermore, they provide a wide range of items which enlarges the rating scale's scope of applicability. Young or acute patients may manifest behaviour which is ordinarily not shown by older "chronic" patients. The wider range permits multiple facets of the patient to be rated progressively as his behaviour improves or changes radically.

Analysis of the chi square tests for the individual items in each split-half (N=28) showed the following extent of agreement between the results of the two experiments: one item significant at the $< \cdot 001$ probability level for both experiments (No. 41), seven at the ·05–·01 level (Nos. 31, 84, 90, 93, 46, 29, 6), and seven at the ·10–·06 level (Nos. 87, 78, 42, 80, 35, 77, 44). Twenty-seven attained the ·30–·11 level of significance and 58 fell below the ·30 probability level in both experiments. In résumé, fifteen items were significant in both experiments at the ·10 level or better (Nos. 41, 31, 84, 90, 73, 46, 27, 6, 87, 78, 42, 80, 35, 77, 44). Considered from the viewpoint of the *total* group (N=56), one item of these fifteen was significant at the ·01 level and the rest at the $\leq \cdot 001$ level of probability. Since these fifteen items were the most effective of the scale, they led logically to the possibility of a short form of the ABRS. The original three experiments were therefore repeated, this time with scores derived only from the fifteen more effective items. Highest possible score was 15, and lowest was 0. Results of the three experiments are reported in Table III.

The chi square test of independence between ward adjustment and ABRS score based upon the fifteen most effective items cited above, led to rejection of the null hypothesis ($\chi^2 = 41 \cdot 34$, $P < \cdot 001$, N=56). The coefficient of contingency, corrected for broad categories, was ·95. There is no doubt that the abbreviated scale of fifteen items was exceedingly effective in differentiating between the two criterion groups. This was true for the replication as well as for the total group.

Rank order correlations were determined between the total ABRS scores and the scores derived from the abbreviated scale of fifteen items. Rho was ·92 for the twenty-eight patients on ward 10C. It was ·92 for another sample of twenty-eight patients, fourteen from the better adjusted ward 9D (even-

TABLE III

*Behavioural Rating Scale (15 Items) Comparative Data Ward 10C VS 9D*

| Patients | Mean | t | P | Variance | F |
|---|---|---|---|---|---|
| 10C (odd) (N 14) .. .. .. | 3·50 | | | 153·50 | |
| VS .. .. .. | | 6·07 | <·001 | | 1·35* |
| 9D (odd) (N 14) .. .. | 10·85 | | | 113·68 | |
| 10C (even) (N 14) .. .. | 3·50 | | | 115·50 | |
| VS .. .. .. | | 7·62 | <·001 | | 1·45* |
| 9D (even) (N 14) .. .. | 11·35 | | | 79·18 | |
| 10C Total (N 28) .. .. | 3·50 | | | 269·00 | |
| VS .. .. .. | | 9·74 | <·001 | | 1·38* |
| 9D Total (N 28) .. .. | 11·10 | | | 194·68 | |

* Not significant at 5 per cent. level of confidence.

numbered) and fourteen from the poorly adjusted ward 10C (even-numbered). The significance of the correlations is two-fold: (*a*) the short and long forms of the ABRS are closely related, and (*b*) the correlation is high despite the presence of a narrow "range of talent". An independent sample drawn from one intensive treatment ward yielded a rank order correlation of ·88 (N=21) between the total ABRS and its short form of fifteen items.

*Readability*. A primary goal in the development of the scale was good readability. This, together with rapid administration and effective scoring, would render it suitable for clinical use by nursing and rehabilitation personnel. Special attention was therefore given to its structure.

Flesch's new readability yardstick (1948) was applied to the total scale. This provided two scores, the "reading ease" index and the "human interest" score. The intrinsic value of the latter lies in its heightening of the reader's attention, and its strengthening of his motivation to comprehend the content. Table IV presents results of the separate readability analyses for the instructions and the content of the Albany Behavioural Rating Scale.

TABLE IVA

*Reading Ease Score (Flesch), Behavioural Rating Scale*

| | Score RE | Description | Equivalence |
|---|---|---|---|
| Instructions .. .. | 73·0 | "Fairly Easy" | Slick-Fiction |
| Scale Content .. .. | 65·5 | "Standard" | Digests |

TABLE IVB

*Human Interest Score (Flesch), Behavioural Rating Scale*

| | Score | Descriptive Standard | Equivalence |
|---|---|---|---|
| Instructions .. .. | 43·8 | Highly Interesting | "New Yorker" |
| Scale Content .. .. | 37·4 | Interesting | "Readers Digest" |

According to standards developed by Flesch, reading ease scores may range from 0 to 100 or "Very Difficult" to "Very Easy". Similarly, human interest scores range from 0 to 100 or "Dull" to "Dramatic". Considered from this standpoint, the instructions for the ABRS were "Fairly Easy" and similar to the reading ease of Slick-Fiction. Their human interest score was "Highly Interesting" and equivalent to a magazine such as the *New Yorker* in readership interest. The ABRS content was "Standard" in reading ease and similar to the style of the *Reader's Digest*. On the basis of this analysis, it may be concluded that the scale meets the criteria cited above: ease of readability and interesting content. Nurses, aides, or rehabilitation personnel can readily apply this scale to problems of ward behaviour and of interpersonal communication.

From Table II and associated text, it was apparent that some items were more diagnostic of the criterion than others when they were considered individually. All were retained in the scale to give it broader scope, although a short scale of 15 items was made available (Table III, text, and Appendix A). Investigations of validity ordinarily show little benefit from differential weighting of items in long tests.

The possibility was tested, that a more complex system of weighting the items of the full rating scale might lead to greater validity. A method was adapted from Guilford (1950), utilizing his abac for graphic determinations of the scoring weights for responses to each of the 100 scale items. Each item thereby received a weight of 1, 2, 3 or 4; 1 signified no differentiating power and 4 signified the most powerful differentiators.

A fresh sample of scales was obtained and scored for twenty long-term patients. They were scored by the previous, simple method of 0 or 1 for each item in accordance with the "unhealthiness" or "healthiness" of the rating. They were again scored by the complex weighting system of 1 through 4. In the first instance the median was 30·5, range 16–66. In the second, it was 57·5, range 28–138. A rank order correlation was computed, yielding rho at ·99. This correlation was so high as to show that no change ensued as a result of the new scores based on complex weightings. The rating scales of the original 9D criterion patients were also rescored with the new weightings. The obtained median was 126 with range 52–195. Under the simple scoring system it had been 59·5 with range 30–87. A Pearson correlation coefficient was computed between these two sets of scores. R was ·95 (N=28), once again so high as to indicate negligible difference in results from the complex weighting procedure as against the simplified system. Finally, the 9D criterion group of relatively well adjusted mental patients (N=28) was tested against a new sample of relatively poorly adjusted patients (N=20) similar to the first 10C criterion group in ward behaviour. Chi square tests of independence were conducted (N=48) for scores derived from the complex weighting system, and again from the simple system. Results are reported in Table V. Partition points for the chi square tests were set *a priori* at the medians for the total scoring ranges.

TABLE V

*Behavioural Rating Scale*
*Comparative Effectiveness of Weightings*

| | Simple Weightings | | | Complex Weightings | | |
|---|---|---|---|---|---|---|
| Patients | Chi Square | P | Phi | Chi Square | P | Phi |
| "Better" Adjusted (9D) (N=28) VS "Poorly" Adjusted (10C) (N=20) | 41·16 | <·001 | ·93 | 41·16 | <·001 | ·93 |

The two scoring systems gave identical results. Both were unquestionably effective in discriminating anew between the criterion groups; the complex system did not yield an increment in power. It is therefore suggested that the simple item weights, 0 or 1, be retained and used additively to constitute the total scale score.

In view of the fact that validation study was based upon differentiation of groups of long-term psychotic patients, these findings are most applicable to the use of the scale for research with and study of groups of patients.

## CONCLUSIONS

The Albany Behavioural Rating Scale demonstrates the following characteristics:

(*a*) Adequate rater reliability, and test reliability.
(*b*) Appropriate validity in reflecting the ward adjustment and social communication of psychotic or long-term mental patients.
(*c*) Easily applied and rapidly key-scored.
(*d*) High correlation with its short form composed of fifteen effective items.
(*e*) Reading ease and human interest consistent with clinical utilization of the scale by nursing and rehabilitation personnel.

## SUMMARY

The Albany Behavioural Rating Scale (ABRS) was developed to provide a rapid and effective method for rating the ward adjustment and social behaviour of psychotic or long-term mental patients. It consisted of 100 items covering six areas: Self Care, Orientation, Communication and Socialization, Psychotic Behaviour, Co-operation, and Reaction to Environment. Scores ranged from 100 (healthiest) to 0 (least health).

Two independent reliability studies with two different pairs of raters showed adequate consistency between raters: rank order correlations ·79 (N=31) and ·84 (N=25) respectively.

The ABRS was evaluated by t-test for its ability to differentiate between the patients of two contrasted wards. The mean ABRS scores obtained by the patients of two contrasted wards were significantly different and in the expected direction (P< ·001). This was true for the split-half replications (N=28) as well as for the total (N=56). A chi square test of independence led to a contingency coefficient of ·60, with rejection of the hypothesis of independence (P<·001).

Each item of the ABRS was tested by chi square for its ability to differentiate between the criterion wards. This was performed as a replication experiment. Fifty-five items differentiated significantly at the 5 per cent. level of probability or better (< ·05) in at least one of the split-half experiments or in the total. Fifteen items were significant in both split-half experiments (P< ·05). These fifteen items were studied as a possible short form of the ABRS. Scores derived from the short form were effective in differentiating the patients of the two criterion wards. This was demonstrated on the previous sample, as a replication experiment. Coefficient of contingency was ·95 (N=56), with hypothesis of independence rejected at the < ·001 confidence level. Correlation (rho) between the short and long forms was ·92 for each of the split-halves, and ·88 for an independent sample (N=21).

Analysis of reading ease and human interest, according to the Flesch criteria, showed suitable ABRS readability for clinical use by nursing and rehabilitation personnel.

A complex weighting scheme was developed in accordance with the differentiating power of the individual items. This was highly correlated with the previously utilized simple score schemes. The application of the scale to a new criterion group again demonstrated its validity for this purpose. Complex and simple weighting schemes, both differentiated the new criterion group in identical fashion (P< ·001, phi coefficient= ·93, N=48). It was therefore suggested that the simplified scoring method be retained.

It is concluded that this scale is valid for the rating of groups of psychotic or long-term mental patients, shows appropriate rating reliability, and is highly correlated with its short form. It is readable, quickly scored, and suitable for ward use.

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## APPENDIX A

Contains items adapted and reprinted from Hospital Adjustment Scale by James T. Ferguson, Paul McReynolds and Egerton L. Ballachey with the permission of the authors and of the publishers, Stanford University Press. Copyright 1953 by the Board of Trustees of Leland Stanford Junior University.

### Scale for Rating Patients' Behaviour
### (Revised Research Form)

Introduction: This Scale will aid you in describing the behaviour of the following patient:————————————, Ward————————. The Scale is composed of 100 statements which characterize some of the ways that various patients behave on a neuropsychiatric ward.

Before each statement you will see Yes No. Mark a circle around Yes if the statement is generally true for the above named patient. Circle No if the statement is generally not true for the above named patient. Please base your circling of Yes or No on your observations of the above patient for the past two weeks to three months.

Please answer the following questions:

What is your name and title?————————————————————————

How long have you known the patient?————yrs.————mos.————wks.

You are to mark *each* statement. Therefore, you may need to observe the patient more or obtain the information for certain statements in the Scale from other hospital personnel.

Be Sure You Mark Each Item. Don't Leave Any Out

Simple weighting: score 1 for each item rated in "healthy" direction.

Complex weighting: as indicated for each item rated in "healthy" direction.

Write down what time it is now————————a.m.————————p.m.

1. (Yes) No The patient knows who he is. ("Healthy" complex weighted score 1)
2. (Yes) No The patient sleeps well. (1)
3. Yes (No) The patient ignores the activities around him. (3)
4. Yes (No) Has hallucinations. (3)
5. Yes (No) Must be helped along to stick to any activity. (3)
6. * Yes (No) Swears and uses obscene language. (3)
7. (Yes) No Writes sensible and understandable letters. (3)
8. (Yes) No The patient makes his own bed. (3)
9. (Yes) No Follows events in the daily paper. (2)
10. (Yes) No Plays cards occasionally. (2)
11. (Yes) No Asks if there's work to do. (3)
12. (Yes) No Laughs if he is kidded. (1)
13. Yes (No) The patient stays by himself. (1)
14. Yes (No) Has to be dressed. (1)
15. Yes (No) Has to be reminded to attend to routine. (2)
16. (Yes) No The patient chooses to talk only to the personnel or to patients who talk sensibly. (3)
17. Yes (No) Has frequent changes in mood. (3)
18. (Yes) No Asks to leave the hospital to visit his family. (2)
19. (Yes) No Makes distinctions between new and old personnel. (1)
20. Yes (No) Needs supervision on a job. (3)
21. Yes (No) Is sloppy. (2)
22. (Yes) No Mixes with other patients. (2)
23. Yes (No) Is constantly moving about. (1)
24. (Yes) No Takes part in back and forth conversation. (3)
25. (Yes) No Talks about sports with an aide or nurse. (3)
26. Yes (No) The patient resents it if he is asked a question. (3)
27. *(Yes) No Is happy. (Do not include psychotic or hebephrenic laughter.) (1)
28. (Yes) No Can tease other patients back into good humour. (1)
29. (Yes) No Shaves himself. (3)
30. Yes (No) Has to be pushed to follow routine. (1)
31. *(Yes) No Answers sensibly if talked to. (3)
32. Yes (No) The patient has delusions. (Queer ideas.) (1)
33. Yes (No) The patient is slow. (1)

34. (Yes) No Has close friends on the ward. (3)
35. * Yes (No) Yells at aide when he is dissatisfied. (3)
36. (Yes) No Eats well. (3)
37. Yes (No) Is backward about talking to you. (2)
38. (Yes) No Reacts to entertainment. (2)
39. Yes (No) Makes sexual passes at other patients. (1)
40. (Yes) No Will discuss many subjects. (2)
41. *(Yes) No Wants to do the right thing on the ward. (4)
42. *(Yes) No Always combs his hair. (3)
43. Yes (No) The patient sits all day. (1)
44. *(Yes) No Reads newspapers and magazines. (3)
45. (Yes) No Does any extra chore. (2)
46. *(Yes) No You can hold his attention. (3)
47. (Yes) No Likes to change his clothes. (2)
48. (Yes) No Takes part in ward games. (2)
49. (Yes) No Is making realistic plans for when he leaves the hospital. (1)
50. (Yes) No Behaves exceptionally well when taken off the ward. (2)
51. (Yes) No Knows the names of doctors, nurses, and aides. (1)
52. (Yes) No The patient recognizes that he is mentally ill. (1)
53. (Yes) No Takes part in athletics. (1)
54. (Yes) No Is interested in O.T. (3)
55. (Yes) No Talks about his family with the aide. (2)
56. (Yes) No Takes pride in his personal appearance. (2)
57. (Yes) No Takes part in recreation. (2)
58. (Yes) No Likes to go for exercise. (2)
59. (Yes) No The patient sometimes remarks when it is time for a family visit. (1)
60. (Yes) No Always attends ward parties. (2)
61. Yes (No) Easily becomes upset when things don't suit him. (2)
62. Yes (No) Repeats words and phrases in a meaningless and mechanical manner. (3)
63. (Yes) No Starts conversation with aides to become better acquainted. (3)
64. (Yes) No Is very interested in his clothes. (3)
65. (Yes) No Is a good worker. (3)
66. (Yes) No Often volunteers information about himself. (2)
67. (Yes) No The patient seeks things to do for recreation. (3)
68. Yes (No) Tries to injure himself. (1)
69. (Yes) No Maintains a correspondence. (3)
70. Yes (No) Does the opposite of what he is asked to do. (2)
71. (Yes) No The patient is able to bathe and shower himself. (1)
72. (Yes) No Writes letters. (3)
73. * Yes (No) Is oriented to time. (3)
74. Yes (No) Is assaultive. (1)
75. (Yes) No Enjoys being talked to. (3)
76. Yes (No) Chews or swallows things other than food. (1)
77. *(Yes) No Stays neat and clean. (3)
78. *(Yes) No Talks over happenings on the ward with the aide. (3)
79. Yes (No) Talks to himself. (1)
80. * Yes (No) Is resistive. (3)
81. (Yes) No Plays ball with other patients. (1)
82. (Yes) No Is oriented to place. (3)
83. Yes (No) Wets himself. (1)
84. * Yes (No) The patient is either silent or talks foolishly during visits. (2)
85. Yes (No) Always asks for things, he never waits for things to be given to him. (1)
86. Yes (No) Maintains manneristic postures and movements. (3)
87. *(Yes) No Chats with other patients. (3)
88. Yes (No) Plays with his penis. (1)
89. Yes (No) Is irritable and grouchy. (2)
90. *(Yes) No The patient's words are always understandable. (3)
91. Yes (No) Needs supervision with dressing. (1)
92. Yes (No) Soils himself. (3)
93. (Yes) No Will always reply if you make some remark to him. (2)
94. (Yes) No Is interested in things. (2)
95. (Yes) No Is co-operative. (2)
96. (Yes) No Asks for a pass. (Short stay away from the hospital.) (2)
97. Yes (No) Has trouble remembering. (3)
98. Yes (No) Clothes are unbuttoned. (3)
99. Yes (No) Would sit all day unless directed into activity. (1)
100. Yes (No) Usually looks tired and worn out. (2)

# SODIUM AMYTAL AND EYELID CONDITIONING*

By

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## INTRODUCTION

SODIUM amytal has long been regarded as a physiologically inhibiting drug. It is widely used in clinical practice as a sedative and sleep-producing drug, although all of its precise pharmacological effects are not definitely established. It has also been suggested that sodium amytal produces an increase in extraversion, as manifest by an increase in communicativeness, etc. Thus Lindemann (1932) found that after receiving amytal, normal subjects report feeling of increased well-being, co-operativeness, serenity and friendship. Sodium amytal is also used for the reduction of manifest anxiety. Sargant and Slater (1954) cite many examples of its use for this purpose with neurotic subjects; they describe it as useful for "deconditioning to situations likely to produce anxiety". Masserman (1938) reports that amytal apparently reduces the sympathetic activity in cats which normally results from faradic stimulation from the hypothalamus. It has also been shown to abolish conditioned fear responses in kittens (Bailey and Miller, 1952).

The literature related to conditioning is enormous. Hilgard and Marquis (1940) alone have a 973 item reference list at the end of their book. It has been established that anxiety neurotics or anxious subjects condition better than normals (e.g. Welch and Kubis, 1947a, 1947b; Taylor, 1951; Spence and Taylor, 1953; Spence and Farber, 1953). In the terminology of Eysenck (1952, 1953), in which introversion–extraversion and neuroticism are two orthogonal dimensions, anxiety neurotics are part of the groups known as Dysthymics, i.e. they have high scores on both the introversion end of the introversion–extraversion dimension and on the dimension of neuroticism. On the other hand hysterics and psychopaths have been shown to have high scores on the extraversion end of the introversion–extraversion dimension and on the dimension of neuroticism. Figure 1 will make this clear.

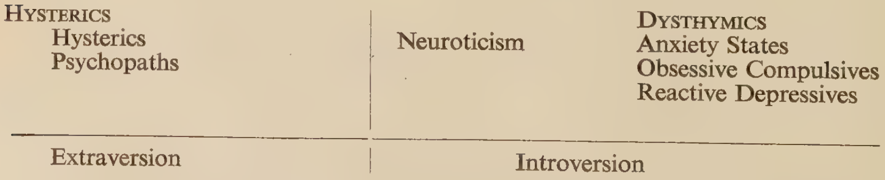

FIG. 1.—The Orthogonal Dimensions of Introversion–Extraversion and Neuroticism.

It is possible that anxiety states could condition well because they are introverted or because they are neurotic. It is possible to investigate these possibilities by a critical experiment. If conditioning is related to neurosis then hysterics, psychopaths and dysthymics all condition well; if conditioning is related to introversion, then only the dysthymics should condition well and the hysterics and psychopaths should condition poorly. This experiment has been carried out and it was found that conditionability is related to introversion–extraversion and not to the degree of neurosis (Franks, 1955a). This finding is an elaboration of a profound observation by Pavlov (1927, p. 397f) made over a quarter of a century ago and largely neglected ever since. He postulated that hysterics possessed an exaggeration of the "inhibitory process" and that neurasthenics had an exaggeration of the "excitatory process". Since he had also established that dogs with an exaggeration of the inhibitory process conditioned poorly and that dogs with an exaggeration of the excitatory process condition readily it is possible to predict that hysterics should condition poorly and that anxiety states should condition readily.

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* The authors are indebted to Mr. A. S. C. Ehrenberg for his advice in designing the experiment and analysing the data.

It would seem possible, therefore, that on a more fundamental level both introversion–extraversion and conditionability are related to the cortical processes of excitation and inhibition, as conceived by Pavlov (1927, 1928, 1941). If this is so, then a drug which increases cortical inhibition should decrease conditionability and increase extraversion. One of the effects of sodium amytal would seem to be that of a cortical depression. Hence it may be predicted that this drug would reduce conditionability* and increase extraversion. As far as the present writers are aware this hypothesis has not been previously tested, although it has been shown (Hilgard and Marquis, 1940, p. 119) that other depressants, such as sodium bromide, retard the rate of conditioning and accelerate the rate of extinction.

## SAMPLE

The present study was carried out upon 16 neurotic hospitalized subjects, of either sex, diagnosed as dysthymics (anxiety states, obsessive compulsives, reactive depressives) and therefore expected to condition readily. Care was taken to exclude subjects who had, over the week preceding testing, been receiving barbiturates as a nightly sedative and subjects who were known to have any kind of brain injury. Subjects with any suspicion of psychotic traits were also excluded. All of the subjects were between the ages of 17 and 46 and none were of dull intelligence. Unlike a previous study in conditioning (Franks, 1954, p. 173–188) no attempt was made to reject those patients who had tendencies towards extraversion, as measured by the attainment of a critical score of 33 on a questionnaire test of extraversion, namely Guilford's R scale (Guilford and Guilford, 1939).

## TREATMENTS

Four different treatments were used, two of these consisting of different doses of amytal, one of a placebo and one of no drug or placebo. The problem of dosage has been considered by Goodman and Gilman (1941) who conclude that "when barbiturates are injected intravenously it is difficult to judge in advance the amount to be given . . . reliance cannot be placed on fixed doses based on age and weight . . . individuals vary in their response" (p. 85). Because of this it was thought necessary to compare the effects of two different doses of the drug, one sufficiently large so that one could be reasonably certain of a definite clinical effect, and an appreciable smaller dose such that while marked clinical effect might not be readily apparent some effect could still be expected during the testing and clinical observation. There is some published guidance as to the magnitude of dosage required for these purposes. For example, Thorner (1935) found that 7·5 grains injected intravenously over a period of 4–5 minutes produced narcosis in two large groups of mentally sick subjects. His subjects comprised many kinds of diagnoses, including neurotic, psychotic and organic states. Among other findings was that patients with organic brain damage required smaller doses of amytal for narcosis to appear. Personal experience with drugs by the medical author of this paper suggests that a dosage of a ½ grain per stone body weight in dysthymic type of patients is most likely to produce the desired effects without producing sleep. It was therefore decided that the four different treatments of the present study would be constituted as follows:

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* Another effect of sodium amytal is to reduce the sympathetic activity of the autonomic nervous system. Now Spence and his colleagues (Spence and Taylor, 1951; Taylor, 1951; Taylor and Spence, 1952), proceeding within a framework of Hullian theory assume that conditionability is a function of total drive (D) and that variations in manifest sympathetic anxiety really reflect differences in this drive level. Using this theory it is also possible to predict that amytal would reduce conditionability. A way of evaluating the two theories would be to compare the effects of drugs which—as far as is possible—affect the autonomic nervous system only or the cortex only.

(A) A large dose of intravenous sodium amytal. 0·5 grains per stone body weight, made up in a solution of sterile water immediately prior to injection, 1 grain of amytal being dissolved in 2 c.cm. of water, and injected into the right arm at the rate of 2 c.cm. per min. (i.e. at a rate of 1 grain per minute).

(a) A smaller dose of intravenous sodium amytal. This dose was always 2 grains less than the larger dose would be for that subject, made up and injected as above.

In practice the dosage range for the 16 subjects varied from 4 to 6 grains for "A" and from 2 to 4 grains for "a".

(P) A placebo injection of distilled water. This was injected in precisely the same manner and under the same conditions as the sodium amytal. A placebo injection was included in the experimental design since it has been suggested (Lewis, 1941, p. 271) that much of the effects of intravenous barbiturates is suggestive in origin.

(N) No injection at all.

More than one treatment and testing session should be allocated to each subject so that treatment comparisons can be made within each person. For administrative reasons only two sessions were allowed, the second session taking place 5 to 7 days after the first. Care was taken to ensure that at no time was the subject given any indication of which treatment he was about to receive or had received (except in so far as the subject was naturally aware that he was receiving neither drug nor placebo). The participation of the subjects was voluntary, and they were told that the purpose of the investigations was to discover whether the unknown drug would help them to relax or not.

## PROCEDURE

The procedure was as follows: The subject was placed on a couch in a nearby room and the appropriate treatment administered. The subject was then taken into the sound-proof conditioning laboratory (Franks, 1955b) and exactly seven minutes were allowed to elapse between the withdrawal of the needle and the start of the conditioning session. As well as standardizing the experimental situation this time interval allowed the subject to become acclimatized to the sound-proof conditioning laboratory and allowed the experimenters time to adjust the conditioning apparatus, etc. After the conditioning session was completed—approximately 25 minutes—the subject was given a brief interview. The questions asked included such items as "Did you feel sleepy?" "Was it hard to keep still?" The subject was also asked questions concerning how he felt, what effects he thought the drug had upon him, whether he felt conditioned (so phrased that the subject was not helped to realize the nature of the study, if he did not already know) and what his reactions were to being enclosed in this sound and daylight proof room.* The subject was then asked to sort certain personality questionnaires of Guilford (1940). Included in these personality scales were the Rhathymia scale (R), the Socal Introversion scale (S), Depression scale (D) and the Cycloid Disposition scale (C). According to Guilford the R scale differentiates the habitually gloomy individual from the cheerful and optimistic; and the C scale differentiates the individual with strong emotional fluctuations from the person with an even disposition and stability of mood. Eysenck (1953, p. 107) considers that D and C are largely measures of a personality factor of general neuroticism and that R is largely a measure of extraversion. The method of administration was different from that used by Guilford. Each item was typed on a separate card and the subject had to "post" these cards into one of three boxes labelled YES, ?, and NO. Finally the subject was given the Maudsley Medical Questionnaire, which consists of 40 "neurotic" items and 18 Lie scale items. Eysenck (1952, p. 94ff) discusses this questionnaire extensively and concludes that, given good subject motivation, it differentiates between neurotics and normals very well.

The sound-proof conditioning laboratory and conditioning procedure has been described in detail elsewhere (Franks, 1954). It is sufficient to state here that the unconditioned stimulus was a puff of air, delivered to one eye at a pressure of approximately 65 mm. of mercury from a distance of 2 cm. from the eye and lasting 500 milliseconds. The conditioned stimulus was a pure tone of frequency 1,100 cycles per second at an intensity of 65 dB above the subject's auditory threshold (which was first ascertained in the usual manner). The duration of this tone, heard through a pair of padded earphones, was 800 milliseconds. The air puff was so arranged that it began 350 milliseconds after the tone had commenced. Partial conditioning was used, the sequence being such that the reinforcement ratio was approximately 60 per cent. throughout the reinforcement trials. Thirty reinforcement trials were given, interspersed with 18 test trials, consisting of the conditioned stimulus alone. The inter-trial interval varied from 20 to 30 seconds with a mean of approximately 25 seconds. After the 30 reinforcement trials and 18 test trials (called acquisition test trials) had been given the subjects were given a further series of 10 consecutive test trials (called extinction test trials) so that the resistance to extinction could be measured. Throughout the conditioning session the subject sat in a comfortable arm chair with his head on a padded head rest and his feet on a foot rest. As well as being in a sound proof room, the subject was partially enclosed by a small booth, so that his field of vision was almost completely confined to this booth. All stimuli were administered and controlled electronically, the eyelid movements being measured by means of a photoelectric cell

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* The clinical behaviour and body movements of each subject were also recorded. An analysis of these, together with the replies to the various questions asked is to be discussed in another paper (Laverty and Franks, 1955) which deals more specifically with the psychiatric aspects of sodium amytal effects.

(Franks and Withers, 1955). The occurrence of both stimuli and responses was registered on a recording milliameter.

## Experimental Design and Analysis

Since there are four treatments (A, a, P and N) and only two testing sessions a rather complicated experimental design had to be adopted. This is the so-called "incomplete block" (Cochran and Cox, 1950, Chapter II). It is possible to obtain a balanced design using only six subjects (A–a; A–P; A–N; a–P; a–N; P–N), but since for each person test and retest data may differ, this basic design must be repeated, with each pair of treatments (e.g. A–N) in the reverse temporal order (e.g. N–A). Allocation of 12 patients to the 12 pairs of treatment combinations was at random, by means of a table of random numbers.

In addition it was thought worthwhile at this pilot study stage to examine the effects of giving the same treatment at both sessions. Therefore four patients (chosen at random from the initial 16) were given treatment combinations A–A, a–a, P–P and N–N. This subsidiary design can be treated separately from the main experiment and requires no very formal analysis at this stage.

It must be stressed that the experiment is conceived very much as a pilot study, on the one hand to test the main hypothesis (that sodium amytal reduces conditionability and increases extraversion) and on the other hand to give some general information and suggestions upon which more intensive investigations may be based. The experiment was kept so small that even the main hypotheses were unlikely to be confirmed (if true) at a very high level of significance, it being thought wasteful to expend the necessary labour to achieve possible significance with no knowledge of the factors involved.

The basic method of the formal analysis is that of analysis of variance. It is more complicated than for a straightforward design, however, since each subject receives only two of the four possible treatments. Yates's original method of analysis was adopted (see, for example, Cochran and Cox, 1950, pp. 324–25) in which the "treatments" sum of squares and the estimates of the treatment effects have to be specially "adjusted". The analysis of variance gives a residual error variance upon which tests of significance can be based.

The adjusted means (H) for each treatment are calculated from the straightforward means for each of the four treatments by an "adjustment" which allows for the individual differences between persons (since any one person is only given two of the four treatments). The appropriate error variance for a t-test comparing various adjusted treatment means is given in the present instance by $\frac{1}{2}$ (Residual Error Variance in the Analysis of Variance).* If "between persons", i.e. individual differences are insignificant, then adjusted treatment and straightforward treatment will, of course, not differ significantly, therefore either could be used for further analysis. For convenience, the adjusted treatment will be used throughout.

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* Cochran and Cox (1950, p. 325).

$$\text{Effective Error Variance} = \text{Residual Error Variance} \times \frac{k(t-1)}{t(k-1)} \times \frac{2}{r},$$

where k=number of readings per person;
t=number of treatments;
r=number of times each treatment occurs.

## RESULTS

### 1. *Conditioning*

TABLE I

*Number of Conditioned Responses During Acquisition*

| Treatment | Adjusted Treatment Mean (H) |
|---|---|
| A | 2·0 |
| a | 4·0 |
| P | 7·2 |
| N | 7·9 |

The analysis of variance failed to reveal any significant F ratios. The adjusted treatment means are presented in Table I. The residual error variance is 12·0, giving an Error Variance of 6·0 which may be used for testing the primary hypothesis that sodium amytal reduces the number of conditioned responses, i.e. that $H_A$ is significantly less than $H_N$. Using a 1-tailed t-test this is confirmed at the 2·5 per cent. level of significance (the insignificant overall F test for the general treatments effect shows that none of the other treatment comparisons can be significant and therefore they should not be tested).

When the number of conditioned responses obtained during the extinction trials are analysed (Table II) both treatment and persons F ratios are found to be significant at the 5 per cent. level. The test-retest F ratio is not significant.

TABLE II

*Analysis of Variance of Conditioned Extinction Responses*

| Source of Variation | df | Sums of Squares | Mean Squares | F | P Per cent. |
|---|---|---|---|---|---|
| Treatment .. .. .. | 3 | 40·13 | 13·38 | 5·82 | <5 |
| Persons .. .. .. | 11 | 105·83 | 9·62 | 4·18 | <5 |
| Test-retest .. .. .. | 1 | 1·5 | 1·5 | — | — |
| Residual .. .. .. | 8 | 18·37 | 2·3 | — | — |
| Total .. .. | 23 | 165·83 | | | |

The adjusted treatment means for the extinction data are presented in Table III.

TABLE III

*Number of Conditioned Responses During Extinction*

| Treatment | Adjusted Treatment Means (H) |
|---|---|
| A | 0·1 |
| a | 1·9 |
| P | 3·8 |
| N | 3·9 |

When t-tests are carried out as before on the differences between the adjusted treatment means it is found that $H_A$ is significantly less than $H_N$ (2·5 per cent.), or $H_P$ (2·5 per cent.). There is no significant difference between $H_A$ and $H_a$ or between $H_N$ and $H_P$.

The correlation between the number of acquisition conditioned responses and the number of extinction conditioned responses is high and positive (·79). This is in agreement with earlier results (Franks, 1954, p. 261), using the same techniques, apparatus and similar subjects. It is considerably different from the results obtained from Humphreys (1943), who found that acquisition and extinction scores for the eyelid reflex were not highly related.

The conclusion from the analysis of acquisition and extinction conditioned response frequencies so far is that sodium amytal apparently reduces the number of conditioned responses during both acquisition and extinction. Despite the high correlation between acquisition and extinction measures, the data suggest that as far as eyeblink conditioning is concerned resistance to extinction appears to be a more sensitive measure of the effects of sodium amytal than is the number of acquisition conditioned responses. No significant differences between the two dosages were obtained, but the trends in the adjusted means for both acquisition and extinction data are consistent with the possibility that conditionability is some undetermined negative function of the size of the dose administered. This finding may be obscured by both the small number of cases studied and the small difference in size between the two doses used. Interpretation of the data is also complicated by the possibility that different intensities of barbiturates may have different physiological effects (Brazier and Finesinger, 1945).

There were no significant differences in conditionability between subjects receiving a placebo injection and those receiving nothing at all, so that, as far as conditioning is concerned, the effects of sodium amytal cannot be considered due to suggestion.

The results for the 4 persons given the same treatment at each session are presented in Table IV.

TABLE IV

*Conditioned Responses When the Subject is Given the Same Treatment Twice*

| | Average Number of Conditioned Responses | |
|---|---|---|
| Treatment | Acquisition | Extinction |
| A–A | 5 | 1 |
| a–a | 12 | 1·5 |
| P–P | 15 | 7·5 |
| N–N | 14·5 | 8 |

These results are in agreement with the above conclusions. The fact that the general level of responding is higher than in the main experiment is most probably a result of random selection of subjects since this higher level of responding occurs in the first testing session as well as in the second.

TABLE V

*The Relation of Treatment Effects to Rest-Retest*

| | Acquisition | | Extinction | |
|---|---|---|---|---|
| | Session 1 | Session 2 | Session 1 | Session 2 |
| Mean Number of Conditioned Responses for A or a .. .. | 3·7 | 3·7 | 1·5 | 1·0 |
| Mean Number of Conditioned Responses for P or N .. .. | 4·7 | 10·2 | 2·8 | 4·3 |

The relation of treatment effects to test-retest was investigated in the form suggested by the data, namely by comparing all A and a effects on session 1 with all A and a effects on session 2 and similarly for P and N. As Table V suggests the expected* increase in conditioning from test to retest under treatments P and N is not apparent when the subjects receive amytal. This tendency is evident for both acquisition and extinction conditioned responses. Rough tests of significance based on the direct scatter of each set of 6 readings of which these are the means show that for both acquisition and extinction responses the P and N second session means are significantly greater than the other three means which obviously do not differ appreciably among themselves.

In assessing the likelihood of this effect being real or spurious it must be remembered that the sample is very small. A future experiment will therefore be required to confirm the existence of this effect. If confirmed, it may mean that amytal has no direct effect on conditioning, but only restricts the usual retention effects which appear in the retest situation. The possibility that sodium amytal has a cumulative effect here, reducing the ability to form conditioned reflexes upon the second session, is unlikely because the low scoring on the second testing under amytal occurred whether or not the patients had received amytal during the first session.

### 2. *Introversion–Extraversion*

TABLE VI

*Effect of Treatment on Guilford's Scales S and R*

| | Adjusted Treatment Means (H) | |
|---|---|---|
| Treatment | Social Introversion (S) | Extraversion (R) |
| A .. .. .. .. | 38·7 | 33·5 |
| a .. .. .. .. | 29·9 | 37·8 |
| P .. .. .. .. | 36·7 | 22·7 |
| N .. .. .. .. | 32·9 | 23·2 |

The analysis of variance, as expected, produces no significant test-retest F ratio for either social introversion (S) or extraversion (R) scales. The treatment F ratio is significant at the 1 per cent. level (F=12·0) for the R scale. It is not significant for the S scale. When t-tests are carried out on the adjusted treatment means (H) of the extraversion scale scores (R), using the residual error variance (19·1) it is found that $H_A$ is significantly greater than $H_P$ or $H_a$ ($p<0\cdot5$ per cent.). $H_A$ and $H_a$ do not differ significantly, neither do $H_N$ and $H_P$. It would seem then that the hypothesis that sodium amytal increases the scores on Guilford's R scale measure of extraversion is confirmed although a corresponding decrease in social introversion (S) was not observed—possibly because S is not such a good measure of the dimension of introversion–extraversion as is R (Eysenck, 1953, p. 107). This need not necessarily mean that the subjects actually become more extraverted since it may be that they fail to answer the personality scale cards objectively when under the influence of amytal.†

The results for the four persons given the same treatment at each session are presented in Table VII.

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* An increase of this order has been found in a study of normal subjects using the same apparatus and conditioning technique, but no injections (Franks, 1954, appendix No. 3, Table 20).

† In the authors' other paper (Laverty and Franks, 1955) the possibility that subjects tend to put more cards in the YES box under amytal is examined. The scales may be so framed that answering YES indiscriminately may have a differential effect on the final scores, affecting some scales, such as R, more than others. It is impossible, owing to the method of scoring used in the present study, to resolve this problem further.

TABLE VII

*Scores on Guilford's S and R Scales when the Subject is Given the Same Treatment Twice*

| Treatment | Average S Scale | Score on R Scale |
|---|---|---|
| A–A .. .. .. .. | 38 | 31 |
| a–a .. .. .. .. | 30 | 25 |
| P–P .. .. .. .. | 41 | 12 |
| N–N .. .. .. .. | 33 | 29 |

The data presented in Table VII are approximately in agreement with the above conclusions.

## CONCLUDING SUMMARY

The two main hypotheses of this pilot study would seem to be confirmed tentatively. These are (1) that intravenous sodium amytal reduces the number of conditioned eyeblink responses during acquisition and increases the rate of extinction; (2) that intravenous sodium amytal increases the extraversion score as measured by Guilford's R scale.

These two conclusions must be regarded with caution and as requiring further experimental investigation, since the possibilities arise from the data that (1) sodium amytal has no direct effect upon conditioning but only restricts the appearance of the usual retention effects which manifest themselves during retest; (2) the increase in R score (extraversion) after the subject has received intravenous amytal may be, in part at least, a product of an increased tendency to say YES to the questionnaire items while under the influence of the drug.

For no measure were the scores obtained under treatment P (placebo injection) significantly different from the score obtained under treatment N (no injection), neither were any trends in the data evident. It would seem reasonable to conclude that, as far as eyelid conditioning and the personality questionnaires used in the present study are concerned, the effects of intravenous sodium amytal cannot be attributed to suggestion.

Under the conditions of the present study a dosage difference of 2 grains intravenously produces no significant differences in the measures under investigation. The trends in the data however are consistent with the possibility that eyelid conditionability is some undetermined negative function of the size of dose administered.

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# THE EFFECTS OF HABIT TRAINING ON CHRONIC SCHIZOPHRENIC PATIENTS

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## INTRODUCTION

It has been recognized for at least 150 years that the organization of wards in public institutions often "results in a lack of adequate attention, provides an unnatural environment and promotes neglect, abuse, injuries and confusion", Noyes (1953). The atmosphere of the mental hospital back-ward, so different from that existing in the patient's home, creates a social, psychological and physiological "vacuum" and is particularly unfavourable to the long staying schizophrenic patient, who, as a result shows a progressive deterioration in habits and social relationships.

An early remedy practised at the York Retreat (Samuel Tuke, 1813) was that the nurses, having gained the patients' confidence, should attempt "to arrest their attention, and fix it on objects opposite to their illusions; to call into action as much as possible, every remaining power and principle of the mind; and to remember that, in the wreck of the intellect, the affections not unfrequently survive."

These principles are now firmly established in the care of the patient newly admitted to hospital who receives, in addition to physical treatments, the stimulus of occupation, social activities and help in readjusting and returning speedily to the community from which he has come. The need for the continued application of such stimuli in the management of those patients who fail to make a rapid recovery is recognized more frequently and has been forcefully restated by Bickford (1954). The varied means by which this aim can be achieved have in this century been outlined by Simon (1927, 1929), Menninger (1944), Main (1946), Burlingame (1947), Dancik (1952) and Maxwell Jones (1952).

All these authors have re-emphasized the deteriorating effects of idleness in an unnatural environment and the desocializing results of traditional methods of treatment. With varying emphasis they appeal for the encouragement of the personal responsibility of the patient and the provision of adequate outlets for his basic drives in work and play, properly guided, graded and expanded as circumstances permit. In considering the unsatisfactory hospital environment Main (1946) and Maxwell Jones (1952) stress the need to develop a therapeutic community in which all members, both patients and staff, may participate more fully and point out that this involves difficult and painful changes in the traditional staff roles and relationships.

The rehabilitation of those patients already showing desocialization and habit deterioration received a new impetus when Myerson (1939) described a method which he called "Total Push". No new principles were involved in this approach, which took place in the established mental hospital setting and depended on the sustained application of a programme of activities, the stimulation of praise and reward and greater attention to the physical needs of the patient. In this country similar methods, usually described as "Habit Training", have been practised at many hospitals and the programme of training promoted at Warlingham Park Hospital by T. P. Rees has been described by Symons (1951). Although these methods have received increasing recognition, little has been written and no accurate attempt has been made to measure the results.

The recent work in America of Lucero and his colleagues (1952) at Fergus Falls State Hospital and Galioni *et al.* (1953) are the first essays in the assessment of results of "Total Push". In both these experiments behaviour rating charts were used to assess changes in groups of treated and untreated patients. Sines, Lucero and Kamman (1952) studied the results of a six months' programme which included the use of E.C.T. in addition to resocializing activities. Their results described in that paper and in a subsequent follow-up study by Fjeld, Lucero and Rechtshaffen (1953), indicated positive but minimal changes unrelated to the patients' initial behaviour level, length of stay in hospital and diagnostic category.

In 1815 Latham anticipated that "anything, however trivial, upon which his (the patient's) faculties could be exercised, might provide in an incalculable degree towards his comfort, and consequently towards his speedier recovery" (quoted by Rees-Thomas (1949)). The experimental method has at last been brought to bear on this neglected problem and we may hope to discover more clearly what are the important or trivial things which promote the patients' recovery and to calculate the degree to which they are effective.

The investigation described here was intended as a contribution towards this general aim by comparing the effects of habit training, carried out according to the British procedure, on chronic psychotics with changes during the same period in similar patients who did not receive habit training.

## PATIENTS INVESTIGATED

Ten patients of Netherne Hospital were selected at random from a male chronic ward for habit training and ten matched patients from the same ward were employed as an untrained control group. All twenty patients were diagnosed as chronic schizophrenics. All showed some degree of disturbance in perception, language or thought and of disorganization in personal habits. The groups were as closely matched for age and duration of illness as was feasible. They were not matched for original ability, since standard intelligence tests could not be successfully applied to more than one or two of them.

The habit training of the experimental group was begun in June, 1952. An initial assessment of the patients in the two groups was made at that time; they were reassessed after the lapse of one year and again reassessed after the lapse of two years. The initial assessment suggested that the group for training was probably of lower mean original ability than the control group. This suggestion was confirmed when the previous occupational levels of the patients were rated by the system of Goodenough and Anderson (1931). The initial assessment also indicated that, while the two groups were of the same general diagnostic status, the patients in the training group displayed a greater amount of cognitive disturbance, those in the control group a more emphatic disordering of personal habits. None of these three discrepancies reached statistical significance at the 5 per cent. level but in view of the small numbers involved statistical allowance was made for them when comparing the groups.

During the first year one patient from the experimental group was, for clinical reasons, given a course of E.C.T. and one patient from the control group was transferred to another hospital, so that only nine patients were available in each group for the first reassessment. During the second year one patient in the training group died of coronary thrombosis, one developed tuberculosis and one was transferred to another hospital. Two patients in the control group were transferred, for clinical reasons, to the habit training group. For the second reassessment, therefore, there were available six patients in the experimental group and seven patients in the control group. The initial comparability in regard to age, duration of illness, occupational level, cognitive disorganization and habit disorganization of the patients involved in the first and second reassessments is set out in Table I.

TABLE I

*Comparability of Groups*

| | Initial Assessments | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | First Year Comparison | | | | | | Second Year Comparison | | | | | |
| | Trained | | | Control | | | Trained | | | Control | | |
| Variable | N | Mean | Range | N | Mean | Range | N | Mean | Range | N | Mean | Range |
| Age in years | 9 | 38·9 | 27–57 | 9 | 36·0 | 31–44 | 6 | 39·2 | 27–57 | 7 | 36·8 | 31–44 |
| Duration of illness (in years) | 9 | 15·9 | 5–36 | 9 | 14·4 | 10–24 | 6 | 17·0 | 5–36 | 7 | 14·0 | 10–24 |
| Occupational level (Goodenough–Anderson Rating) | 9 | 6·1 | 5–7 | 9 | 3·8 | 2–7 | 6 | 6·2 | 5–7 | 7 | 3·4 | 2–7 |
| Cognitive Disorganization (Pin-man Minus Score) | 9 | 34·2 | 11–48 | 9 | 27·8 | 6–36 | 6 | 29·3 | 11–48 | 7 | 25·8 | 6–36 |
| Habit Disorganization (Nurses' Records: Bad Points) | 9 | 20·8 | 4–36 | 8 | 25·3 | 14–40 | 6 | 19·7 | 4–36 | 7 | 26·8 | 14–36 |

## METHOD OF TRAINING

The method of training was adapted from that developed by J. J. Symons (1951), formerly Chief Male Nurse, Warlingham Park Hospital. The patients followed a strict timetable each day as follows.

| *Hours* | *Activity* |
|---|---|
| 07.15–07.45 | Rising. Dressing, assisted by nurse in charge of group. Visit with nurse to ablutions room to wash, clean teeth, brush hair, etc. |
| 07.45–08.15 | Breakfast under supervision of nurse, all patients in group sitting at tables together. |
| 08.15–09.00 | Personal cleaning and tidying. |
| 09.00–09.45 | Light ward duties under supervision of nurse. |
| 09.45–10.00 | Dress inspection by charge-nurse of ward, with special attention to condition of suit, tie, shirt, socks and shoes. |
| 10.00–11.45 | Rolling grass (Monday, Wednesday, Saturday). Physical training (Tuesday, Thursday, Friday). Free (Sunday). |
| 11.45–12.00 | Changing to slippers. Personal cleaning and tidying. |
| 12.00–12.45 | Dinner under supervision of nurse, all patients in group sitting at tables together. |
| 12.45–13.45 | Personal cleaning and tidying. Putting on shoes. |

| | |
|---|---|
| 13.45–14.00 | Dress inspection by charge nurse of ward, as at 09.45. |
| 14.00–16.00 | Walking in grounds (Monday and Friday).<br>Painting at art class (Tuesday and Thursday).<br>Sports (Saturday).<br>Seeing visitors or free (Wednesday and Sunday). |
| 16.00–16.30 | Changing into slippers. Personal cleaning and tidying. |
| 16.30–17.00 | Tea under supervision of nurse, all patients in group sitting together. |
| 17.00–19.00 | Either light ward duties under supervision of nurse or attendance with nurse at dance, cinema or concert, when available. |
| 19.00–20.00 | Showers or baths (Monday, Wednesday, Friday).<br>Games (Tuesday, Thursday, Saturday). |
| 20.00–20.30 | Personal cleaning and tidying. |
| 20.30 | Retirement to bed. |

In the case of incontinent patients but not the others regular urination and defaecation were supervised by the nurse at the hours of personal cleaning and tidying, i.e. 07.15–07.45, 08.15–09.00, 12.45–13.45, 20.00 and also the additional special hours 24.00, 03.00, 06.00.

The training group were given a special allowance of sweets or cigarettes. The control patients ate, worked and slept in the same ward as the training group but had no special supervision and pursued no regular timetable.

## METHODS OF ASSESSMENT

Five different approaches were used in assessing changes in the patients, viz.:

1. Weight.
2. Scores on a simple information test.
3. Scores on the Pin-man Test of Reitman (1947).
4. Nurses' behaviour records of good and bad points.
5. Interview ratings by one of us (J.P.S.R.), given without knowledge of group membership, as to
    (*a*) Comprehension, communication and self-control.
    (*b*) Personal appearance.

### 1. *Weight*

For this purpose use was made of the routine monthly weighing in the ward, conducted in May, 1952, June, 1953, and June, 1954. Weight was determined in pounds on an Avery weighing machine. The patients were weighed fully clothed one hour after their dinner.

### 2. *Simple Information Test*

The following standard information questions were used at each assessment (i.e. June, 1952, June, 1953, and June, 1954).

(*a*) What is your full name?
(*b*) How old are you?
(*c*) What work do you do in hospital?
(*d*) How long have you been in hospital?
(*e*) What is the name of the doctor in charge of you?
(*f*) Why are you in hospital?
(*g*) What is the name of the medical superintendent?
(*h*) What month is it?

(*i*) What year is it?
(*j*) What county are we in?
(*k*) What political party is in power?
(*l*) What is the name of the present King of England?

These were scored as follows:

*2 marks* The correct answer.
*1 mark* A reasonable approximation.
  e.g. (*g*) Name of former superintendent.
    (*h*) May, July, August.
    (*l*) King George the Sixth.
*0 marks* I. An absurd answer,
  e.g. (*d*) Since seven o'clock last night.
    (*e*) A clever crank who made a drawing for forty million pounds.
    (*l*) Herod. Mercury.
  II. No answer.

(Maximum marks 24.)

### 3. *Reitman's Pin-man Test*

This was applied and scored at each assessment according to the method described by Reitman and Robertson (1950). The plus scores, which range from 0 to 60, measure the extent to which the subject can apprehend and conceptualize emotional expression. The minus scores, which range from 0 to 48, measure the difficulty of abnormal subjects in attending, perceiving, associating, verbalizing, etc., scores on the drawing range from minus 4 to plus 8; the minus values correspond to increasing degrees of cognitive disorder.

### 4. *Nurses' Records of Good and Bad Points*

Each week from the commencement of training the nurse in charge of the group recorded on a special behaviour chart good and bad points for each patient. The good points were: (*a*) keeps with group; (*b*) plays games; (*c*) works; (*d*) works with attention; (*e*) absence of soiling; (*f*) dresses himself tidily; (*g*) cleans himself spontaneously; (*h*) cleans himself when prompted; (*i*) does hair; (*j*) eats food regularly; (*k*) speaks spontaneously to others; (*l*) handles implements appropriately.

The bad points were: (*a*) wanders from group; (*b*) drags in group; (*c*) stands about; (*d*) soils bed; (*e*) soils clothes; (*f*) clothes unfastened; (*g*) clothes dirty; (*h*) destructive to clothes; (*i*) collects rubbish; (*j*) face and hands dirty; (*k*) hair untidy; (*l*) eats waste food or dirt; (*m*) eats with hands; (*n*) gorges unmasticated food; (*o*) refuses food; (*p*) mute; (*q*) abusive or obscene; (*r*) shouts; (*s*) speaks only when spoken to; (*t*) chatters; (*u*) masturbates openly; (*v*) pilfers; (*w*) attacks others; (*x*) destroys; (*y*) handles implements clumsily; (*z*) doesn't handle implements; (*aa*) picks and rubs.

In the case of the controls, "group" was taken to mean "associated patients". Records for the controls were kept by a ward nurse for the first year but, unfortunately, this was omitted in the second year.

For the initial assessment the records of the first fifteen weeks after the beginning of training were employed. For the reassessments the corresponding fifteen weeks a year later and (experimental group only) two years later were used. If a point was noted on eleven to fifteen weeks it was allocated 3 marks, on six to ten weeks 2 marks, on one to five weeks 1 mark. The total marks for good and for bad points were then summed. In the case of good points "plays games" was omitted from the scoring because games were not specially organized for the control group. The overlapping points presented a little difficulty; "works with attention" was taken as implying a point for "works", "cleans spontaneously" as implying one for "cleans when prompted", "doesn't handle implements" as implying one for "clumsy with implements". The range of marks for good points, therefore, was 0 to 33, for bad points 0 to 81.

### 5. *Interview Ratings*

The interview ratings were given at each assessment on the evidence of observations during the Simple Information and Pin-man Tests. As already noted, the interviewer (J.P.S.R.) was unaware which patients were under training and which were not. The rating for comprehension, communication and self-control derived from the elements: (*a*) attentiveness, "attention given to questions and stimuli"; (*b*) comprehension, "understanding of questions and stimuli"; (*c*) general alertness, "efficiency in dealing with problems presented by questions and stimuli"; (*d*) clarity of expression, "clearness of verbal response"; (*e*) self-control, "control of body movements and emotional expression during the examination".

The rating for personal appearance derived from the elements: (*a*) tidiness of hair on head; (*b*) condition of facial hair; (*c*) cleanliness of face; (*d*) cleanliness of finger nails; (*e*) cleanliness of hands; (*f*) tidiness of tie and/or collar; (*g*) cleanliness of jacket; (*h*) cleanliness of trousers; (*i*) attention to trouser buttons, i.e. closed, one button showing, entirely unbuttoned, shirt protruding, etc.; (*j*) cleanliness of shoes.

Each element was rated on a scale:

| | |
|---|---|
| 3 marks | Indistinguishable from normal. |
| 2 marks | Somewhat poor. |
| 1 mark | Definitely poor. |
| 0 marks | Extremely poor. |

The ratings in each section were summed to give the composite ratings for comprehension, communication and control and for personal appearance respectively. The range for the former was 0 to 15, for the latter 0 to 30.

### *Results*

The results of the first reassessment are set out in Table II and those of the second in Table III, in each case in comparison with the initial assessment. The statistical significance of differences in mean gains was tested by analysis of covariance, allowing for the regression of reassessment on initial scores, in order to eliminate the initial discrepancies between the groups already noted. There was no reason to question homogeneity of variance in these comparisons (Variance Ratio test) except in the Good Points of the Nurses' Records. Here the variances were proportional to the means and accordingly the scores were transformed into their logarithms, before the analysis of covariance was carried out.

Since no behaviour records were kept for the control group during the second year, comparison in this regard was not possible at the second reassessment. It is of interest to note that if the status of the experimental group at two years is compared with their initial status they show an increase in good points statistically significant at the 1 per cent. level ($t=4\cdot800$, d.f.5) and a decrease in

TABLE II

*First Year Comparison—Means and Mean Gains*

| | Trained Group | | | | Control Group | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Assessment | | | | Assessment | | | | |
| Variable | N | Initial | First Year | Gain | N | Initial | First Year | Gain | Difference in Mean Gains | Covariance F Ratio |
| Weight (in lbs.) | 9 | 141·7 | 150·9 | 9·2 | 9 | 140·6 | 141·8 | 1·2 | 8·0 | 1·74 |
| Information Score | 9 | 6·0 | 6·9 | 0·9 | 9 | 7·9 | 5·6 | −2·3 | 3·2 | 6·47* |
| Pin-man Figures: | | | | | | | | | | |
| Plus Score | 9 | 2·1 | 5·0 | 2·9 | 9 | 3·6 | 4·4 | 0·8 | 2·1 | below 1 |
| Minus Score | 9 | 34·2 | 30·4 | 3·8 | 9 | 27·8 | 20·9 | 6·9 | 3·1 | below 1 |
| Drawing Score | 9 | −2·8 | −2·7 | 0·1 | 9 | −2·0 | −2·6 | −0·6 | 0·7 | below 1 |
| Nurses' Records: | | | | | | | | | | |
| Good Points | 9 | 17·9 | 24·6 | 6·7 | 8 | 3·4 | 4·8 | 1·4 | 5·3 | 1·58† |
| Bad Points | 9 | 20·8 | 17·1 | 3·7 | 8 | 28·5 | 25·9 | 2·6 | 1·1 | below 1 |
| Interview Ratings: | | | | | | | | | | |
| Comprehension, Communication and Self-control | 9 | 4·9 | 7·9 | 3·0 | 9 | 7·8 | 7·1 | −0·7 | 3·7 | 10·76‡ |
| Personal Appearance | 9 | 23·0 | 21·2 | −1·8 | 9 | 21·2 | 17·7 | −3·5 | 1·7 | 7·14* |

* Significant beyond 5 per cent. point.
† After logarithmic transformation.
‡ Significant beyond 1 per cent. point.

TABLE III

*Second Year Comparison—Means and Mean Gains*

| | Trained Group | | | | Control Group | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Assessment | | | | Assessment | | | | |
| Variable | N | Initial | Second Year | Gain | N | Initial | Second Year | Gain | Difference in Mean Gains | Covariance F Ratio |
| Weight (in lbs.) | 6 | 153·5 | 156·2 | 2·7 | 7 | 140·0 | 134·8 | −5·2 | 7·9 | 2·75 |
| Information Score | 6 | 6·7 | 3·2 | −3·5 | 7 | 9·6 | 9·1 | −0·5 | 3·0 | 1·05 |
| Pin-man Figures: | | | | | | | | | | |
| Plus Score | 6 | 3·2 | 0·2 | −3·0 | 7 | 4·6 | 5·7 | 1·1 | 4·1 | 3·15 |
| Minus Score | 6 | 29·3 | 38·5 | −9·2 | 7 | 25·8 | 23·2 | 2·6 | 11·8 | 3·76 |
| Drawing Score | 6 | −2·5 | −3·3 | −0·8 | 7 | −1·7 | −2·2 | −0·5 | 0·3 | 2·65 |
| Interview Ratings: | | | | | | | | | | |
| Comprehension, Communication and Self-control | 6 | 5·6 | 8·7 | 3·1 | 7 | 8·3 | 7·7 | −0·6 | 3·7 | 2·10 |
| Personal Appearance | 6 | 23·5 | 23·0 | −0·5 | 7 | 21·0 | 17·3 | −3·7 | 3·2 | 12·72* |

* Significant beyond 1 per cent. point.

bad points approaching significance at the 5 per cent. level (t=2·524, d.f.5). If, however, their second year is compared with their first year status the differences in good and bad points are not statistically significant (*t* is less than 1 in both comparisons).

## DISCUSSION

This investigation yields few quite unequivocal findings. The Pin-man results suggest that habit training has no influence on disorders in perception and thought, as no doubt would be expected. There was some reason to suspect an increased food intake and in fact three cases in the trained group showed a marked rise in weight. While the comparative results are not statistically significant the matter seems worthy of further enquiry.

The Simple Information Test and Interview Ratings on Comprehension, Communication and Self-control suggested at the first reassessment that there was a definite improvement in attentiveness, alertness, etc., which could be interpreted as a heightened confidence and interest in other persons or in other words as an increased socialization. In the second year the Information scores declined. The apparent improvement in Comprehension, Communication and Self-control ratings was not statistically significant, but the fact that the trained group did not fall back to their former level should be noted. Possible explanations of the failure to progress further are that the limit of improvement had already been reached or that there was a decreased efficiency in the habit-training procedure, since it is always difficult to maintain nursing interest with changes in staff and in face of the slow and fluctuating improvement.

The differences in personal appearance, although statistically significant, depend on a greater decline in the standard of the control group, not on a positive improvement in the experimental group, and may be an artifact of rating or of the nurses' care.

The nursing staff are strongly of the opinion that the working behaviour of the trained patients has greatly improved in co-operation, initiative and efficiency during the past two years and quote individual examples of this change. The improvement was not expressed in the Nurses' Records and examination of appropriate individual elements (e.g. handles implements clumsily; doesn't handle implements; works; works with attention, etc.) gave no support to such opinions.

Our most decided conclusion is that there should be further investigation, with the weaknesses of the present enquiry amended. The social importance of the problem which habit training is designed to solve certainly indicates that it should receive much more detailed and extensive consideration. The most outstanding weaknesses of the present investigation, we think, were the following:

(*a*) The subjectivity of the records and ratings.

(*b*) The unsatisfactory nature of the Behaviour Charts completed by the nurses, which left certain aspects of behaviour unrecorded and stressed some matters of relatively rare occurrence.

(*c*) The fact that it was not clear how far improvements in personal appearance depended on the patients' own efforts, rather than on the increased intervention of the nurses.

In any future investigation, we think, it is desirable that all ratings, and also recordings which involve an evaluation, should be made by at least three independent judges. We believe that the most satisfactory substitute for the Behaviour Charts of this enquiry would be the L-M Fergus Falls Behaviour Rating Scale described by Lucero and Meyer (1951) and Meyer and Lucero (1953). We also believe that at the end of an agreed period of habit training both experimental and control groups should be observed for a few days during which their personal appearance, conduct of work, etc., depend entirely on their own efforts, without the aid or stimulation of nurses.

With such improved methods of assessment it should be possible to study and compare other methods of rehabilitation.

Possible developments might include the use of larger groups, which would allow the wider application of a method which both by clinical impression and statistical results offers benefit to the chronic schizophrenic patient.

## SUMMARY

1. A brief account is given of the background and history of habit training.

2. An experiment is described in which ten chronic schizophrenics, who were given habit training, were contrasted with ten matched patients who did not receive habit training. Details are provided of the methods of habit training and of assessment of changes in the patients.

3. Clear cut evidence of psychological changes induced by habit training were found in the first year, but this improvement did not continue in the second year. The results left a number of questions open and the need for further investigation is stressed. Certain points requiring special care in further investigations are noted.

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# IRREVERSIBLE HYPOGLYCAEMIC COMA IN ISLET-CELL ADENOMA AND IN SCHIZOPHRENIA

By

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As an approach to the problem of schizophrenia it is proposed to compare the effects and after-effects of severe hypoglycaemia due mainly to islet-cell adenoma of the pancreas in otherwise healthy people with the effects and after-effects of severe hypoglycaemia therapeutically induced in schizophrenics.

The difficulties are plain. Personal experience of patients with functioning islet-cell adenoma is limited almost always to a few cases, whereas average experience of insulin coma treatment covers some hundreds of cases; moreover, there is little overlap of experience except in the post-mortem room or in the laboratory for morbid histology. During insulin treatment there is constant supervision by a trained staff, medical and nursing, so that serious developments can be met by immediate intravenous sugar and investigations are continual; with adenomata there is no observation until, perhaps, a general practitioner is called in about alarming symptoms of one kind or another and sometimes months or even years elapse before a patient gets into hospital, where the intensity of observation and even more so of investigation may exceed that available in mental hospitals. Insulin coma treatment has a more or less standard aim, to produce coma of increasing duration up to a maximum of something like an hour which is then repeated thirty times or more; dosage is built up with the greatest care. Adenomata produce conditions varying from the hardly serious to the fatal under the influence of an insulin dosage which is quite unknown.

This comparison is based chiefly on an analysis of 290 serial courses of insulin coma treatment given to schizophrenic patients at Holloway Sanatorium during the four years 1950 to 1953 inclusive, and on the 258 cases of islet-cell adenoma reported by Crain and Thorn (1949) and the 398 cases, all that could be traced up to that date and including the Crain and Thorn cases, analysed by Howard, Moss and Rhoads (1950). Many separate papers have been consulted for more detailed approaches and for extra information, although of course those published before 1950 were included in the reviews already mentioned. Despite the difficulties of this comparison, it can be shown that the similarities between the two groups follow expectation and are very strong indeed, so that the differences which emerge have at least possible significance.

## GENERAL PICTURE

The general picture of signs and symptoms is in fact indistinguishable. It is not necessary here to review the metabolism of the brain and its dependence on oxygen and glucose, but only to say that both islet-cell adenomata and therapeutic doses of insulin produce the same phylogenetically and ontogenetically determined abrogation of brain function which is familiar, say, in progressive alcoholic intoxication, and that the additional intense autonomic disturbances are also common to both groups. Judgment, reason and clarity of mind are steadily diminished, giving way to increasing drowsiness and clouding and eventually to coma. Before coma blankets them, mental symptoms of every kind, not only excitement and peculiarities of behaviour but symptoms suggestive of almost every psychosis and psychoneurosis (Sigwald, 1932; Greenwood, 1935) can occur, against a background of normality in the case of patients suffering from islet-cell adenoma, added to the symptoms of schizophrenia in the treated patients. Full descriptions are plentiful (Sakel, 1935; Parfitt, 1937; Himwich *et al.*, 1939 and 1941). The march of events is in line with the richer blood supply to grey matter and to correlative centres as compared with motor centres (Wolff, 1936). In both groups sugar ordinarily produces a very rapid disappearance of the abnormal signs and symptoms caused by the hypoglycaemia.

In both groups there is a grave danger of irreversible damage to the brain and of death (the fact that the danger of death is very much greater than that of irreversible brain damage in the case of islet-cell adenomata will be discussed later).

## IRREVERSIBLE COMA

Irreversible coma may be defined as a coma which cannot be terminated at will. Put another way, as a coma which persists while the blood sugar is kept consistently at normal or above normal levels. It varies in severity from case to case, from an anxiety-producing situation lasting several hours to a desperate struggle for life going on through several days, if in fact it does not end in death. There is no detectable difference in this recurring situation as it is described for the severe hypoglycaemia of islet-cell adenoma and as it is described for therapeutic hypoglycaemia, the bedside struggle is the same. The differences are found before the event and more particularly after the event.

It is impossible to make a comparison which would prove that one type of case develops an irreversible coma more easily than another, because such comas are universally possible and the unknowns, particularly in cases of islet-cell adenoma, are too numerous, but one can say that the hypoglycaemic experiences of the undiagnosed sufferers from islet-cell adenoma are often astonishingly severe and that the ease with which serious trouble supervenes in schizophrenia is equally astonishing.

The cases of spontaneous hyperinsulinism reported by Black *et al.* (1954) can be taken as typical. Case 1 would be found unconscious and unrousable in the mornings five to six times a week and there was incontinence and tongue biting, but operation effected a cure. Case 2, a young lady aged 22, after a long and testing period of symptoms was eventually admitted to hospital having been in coma for twenty-four hours. She remained comatose and semicomatose for several days before it was possible to detect that she had developed a left hemiplegia. For some time she was apathetic, unco-operative and emotional, but she returned to her work as a school teacher and had worked steadily for over a year at the time of publication. Case 3 was found unconscious one morning and didn't reach hospital for treatment to begin until four o'clock in the afternoon, but without long-term ill effects. Further confirmation of the prolonged and perilous delays before diagnosis and treatment in non-schizophrenics can be seen in the reports of Layne and Baker (1939), Lidz *et al.* (1949) and Smith and Cochran (1952).

Compare this with by far the commonest setting for an irreversible coma developing during therapeutic hypoglycaemia, which is met in a patient in an acute phase of the malady, suffering a first attack or a further extension of the disease, as a complication of one of the first few comas, when the period of complete coma lasts only a few minutes, in accordance with the usual technique of increasing the length of coma very cautiously because this danger is so well recognized. Including the time consumed by the failure to respond to gastric glucose, the patient is being given sugar intravenously about three hours after the insulin injection and about two and a half hours after the first symptoms of hypoglycaemia, but the most adequate precautions fail and this does suggest a most unusual sensitivity to hypoglycaemia during certain phases of schizophrenia. Marble's (1952) statement, that "the prognosis of an insulin reaction is almost *invariably* good if it is diagnosed reasonably early" (my italics) hardly holds good for this therapeutic complication.

## Post-mortem Findings

It has been shown by laboratory experiments that the brain uses up its reserve of glycogen after about an hour of severe hypoglycaemia and that damage becomes increasingly likely after that (Kety *et al.*, 1948). Yannet's work on cats (1939) suggested a relationship only between damage and excess insulin in the presence of hypoglycaemia, but there is general agreement that in man there is no reliable yardstick provided by dosage, duration of stupor or of coma, sugar level or any other measure (Rivers and Rome, 1944; Malamud, 1948).

The post-mortem findings appear identical and as Ferraro and Jervis say (1939), nothing specific is revealed by the microscope either in the damaged brain or in schizophrenics as compared with others, and for this reason cases of schizophrenia dying under treatment and fatal cases of islet-cell adenoma tend to be mixed indiscriminately. (Malamud and Grosh, 1938; Moersch and Kernohan, 1938; Ferraro and Jervis, 1939; Baker, 1938; Wilder, 1940; Kerwin, 1940; Malamud, 1948.)

Ferraro and Jervis provide a good review and quote other careful studies (Ehrmann and Jakoby, 1929; Terplan, 1934; Bodechtel, 1933; and Wohlwill, 1938), and the reports bring out the great variability and the widespread nature of the damage to the brain, both in animals and human beings. Alterations to blood vessels, with perivascular changes and very numerous cortical and subarachnoid petechiae, which may render the C.S.F. bloody, are usually prominent (Baker; Ehrmann and Jakoby; Ferraro and Jervis; Morsier and Mozer, 1936) and may lead to softening and cysts (Baker). The cortex suffers severe cellular damage and neuroglial changes are prominent, but sometimes the white matter (Mackeith and Meyer, 1939) or the basal ganglia or the cerebellum (Ferraro and Jervis) seem to suffer most. Malamud and Grosh have reported the chief damage in layers 3 and 5 of the cortex, Malamud has described cases where the temporal cortex or Ammon's horn have shown the most severe changes, sometimes it is the occipital and temporal cortex rather than the parietal and frontal, and sometimes the reverse (Ferraro and Jervis), sometimes striking changes in the corpus striatum or in the caudate and putamen are stressed (Malamud). Hassin (1939) saw vital damage in the medulla and the olivary bodies and attention has been drawn to intracellular lipids (Ferraro and Jervis) and the significance of fatty degeneration of the liver has been considered (Malamud). Quoting Spielmeyer (1930), who had a common vascular origin in mind, Ferraro and Jervis mention similarities between the findings and those discovered in epilepsy, eclampsia, pertussis encephalitis, fat and air embolism, occlusion of the carotids and arteriosclerosis, and they add lead poisoning, malaria, serious infections and toxaemias. Jetter and

Sheflen (1952) regard the neuropathological picture of fatal hypoglycaemia as indistinguishable from that of anoxia caused by other agents. I should like to add one further note to this post-mortem evidence of widespread nervous damage. Ferraro (1942) described evidence from three schizophrenics who had died during insulin coma treatment and gave it as his opinion that the cells showed more damage than the vessels and perivascular areas in schizophrenics as compared with normals, and that this cellular damage showed itself "particularly in the frontal and temporal cortex".

### FITS

Fits associated with islet-cell adenomata and with therapeutic hypoglycaemia occur, as far as can be told, with roughly the same frequency. This aspect was reported in some detail by Parfitt (1937) and taking the present series of 290 cases into account as well, the incidence works out at about 50 per cent., but it is very variable. Crain and Thorn reported that 28 per cent. of the 193 cases of which they felt the clinical histories were satisfactory had fits, but only 58 of the 193 became unconscious and only 40 per cent. went into deep coma and it is reasonably certain that the percentage would have been higher if deep coma had been uniform. In such a comparison as is being made here, only the most exceptional differences can be seriously considered.

### MORTALITY

The first unmistakably significant difference is shown by the deaths. Taking the figures of Howard *et al.*, which include those of Crain and Thorn, of 264 *functioning* islet-cell cases, 45 were discovered or confirmed at post-mortem and 15 more died of hypoglycaemic effects, i.e. not from the operation as such or from any other cause, so that there was a death rate of 26 per cent. Two of their own nine cases died. There were no deaths in my 290 cases, although one patient was readmitted to another hospital after discharge and died during the second coma of a new course of treatment. Sargant and Slater (1948) reported no deaths in 400 cases. There have been plenty of deaths during insulin treatment because tens of thousands of patients have been treated, but the death rate is always extremely low as compared with the very high death rate associated with functioning islet-cell adenoma. The death rate for the adenomata is all the more striking when one recalls the 58 per cent. only who became unconscious and the 40 per cent. who reached deep coma, as reported by Crain and Thorn.

Most of the deaths in the islet-cell adenoma cases paralleled the age distribution in general and occurred between 30 and 60, but there were plenty of deaths among young people including children and the enormous difference is clearly due to the difficulty of diagnosis and the perils experienced and damage suffered before hospitalization in the case of islet-cell adenoma as compared with the tremendous care in the use of a known instrument, together with the promptitude of interruption for threatening symptoms associated with therapeutic hypoglycaemia.

### PARESIS AND PARALYSIS

Various forms of transient paresis and paralysis have been recorded as sequels to insulin treatment (Sakel, etc.) but they are uncommon and there were no such sequelae in my 290 cases which averaged 30 or so comas.

Of Crain and Thorn's 193 cases with satisfactory clinical histories 10 per cent. developed hemiplegia, transient in terms of hours or days as a rule although 2 of the Crain and Thorn cases had permanent palsies. These figures are worth stressing, 19 hemiplegias with 2 permanent palsies compared with none. This is very much in line with the deaths. The original smaller series of islet-cell adenomata strengthen the picture. The 9 cases of Howard *et al.*, some of those in their 398 cases considered which were additional to Crain and Thorn's 258, showed 1 permanent hemiplegic and 1 transient paraplegia. Of 6 cases of Bowen and Beck (1933) of which brief clinical descriptions are given, there was a case of transient right sided hemiplegia but *with some residual damage*. Moersch and Kernohan (1938) describe a transient hemiplegia *with permanent weakness of the right hand*, Roxburgh's (1954) young patient had *persisting ataxia*. Tom and Richardson (1951) reported paralysis of all four limbs and wasting of the distal limb muscles. Blau *et al.* (1936) described Parkinsonism with pyramidal signs, ataxia and muscular weakness and Lidz *et al.* (1949) wrote of muscular atrophy and scanning speech. Several patients who died from islet-cell adenoma had obvious paralysis before death, all of which points to the conclusion that even the convincing evidence provided by the hemiplegias reported in Crain and Thorn's series does not fully represent the enormous amount of brain damage suffered by islet-cell adenoma cases as compared with schizophrenics under treatment.

Goodman (1954) has recently described severe hypoglycaemic reactions in 3 diabetics, one of whom suffered a transient hemiplegia four times and one of whom died. Labbé and Boulin (1937) wrote an informative article on hemiplegia occurring in diabetics associated with hypoglycaemia, which is extraneous to the comparison being made, as are Goodman's cases, but which help to throw light on the situation being considered. They described two types of hemiplegia, a transient and a permanent which is possibly fatal. The side paralysed is generally contracted and shows exaggerated tendon reflexes, ankle clonus and a positive Babinski, and if right-sided there is added aphasia; hemianaesthesia is sometimes present. Following intravenous glucose the hemiplegia may disappear in minutes or hours or take several days, the hemiplegia may be repeated and there may be permanent residuals.

Labbé and Boulin draw a further distinction between cases developing as a complication of severe hypoglycaemia and others which are not so important in the connection being examined here which develop more commonly in older people, whose routine has been upset possibly by an infection necessitating more insulin. They doubt whether this kind of hemiplegia, most commonly found in elderly diabetics, can be attributed to the degree of arteriosclerosis but they make the point, an important one in brain pathology, that damaged brain is more susceptible to noxious influences, in this case to hypoglycaemia, quoting Goldstein for their support. Reference to this principle will be made later. Even this surprising type of hemiplegia can occur in young people, Labbé and Boulin describe it in a man of 33 with a history of 4 hypoglycaemic comas who developed right-sided hemiplegia and aphasia which left permanent weakness in the hand and leg, and they refer to other severe hypoglycaemic hemiplegias developing in youths and even young children. Taken by and large, the brain damage occurring as a complication of hypoglycaemia associated with diabetes is more severe than in islet-cell adenoma, if deaths are excluded, because the possibility of repeated incidents cannot be avoided whereas operation for islet-cell adenoma often leads to a cure. One can sum up the situation by stating that there is an overwhelming preponderance of hemiplegic and like phenomena associated with both islet-cell adenomata and with accidental hypoglycaemia in diabetes, as compared with therapeutic hypoglycaemia.

## MENTAL CHANGES

The crucial and most difficult stage of the comparison is now reached.

First of all dementia will be considered. Marble (1952) describes striking cases and others have been reported by Malamud and Grosh, by Wilder, and by Tom and Richardson (1951) of a catastrophic and permanent dementia, a pitiful mindlessness often associated with double incontinence, occurring as a permanent sequel to hypoglycaemia associated with islet-cell adenoma. The incidence would be about 2 per cent. Most of these cases would be included presumably in the series reviewed by Crain and Thorn and by Howard *et al.* Speaking generally such a phenomenon is unknown following therapeutic hypoglycaemia, certainly nothing like it occurred in the 290 cases considered here; the nearest approach to such a picture will be described in some detail, (Case 2), when the differences will become apparent. Crain and Thorn state that of their well-documented series of 193, twelve patients were thought to have irreversible personality changes but seven of them made a complete recovery. The remaining five, again presumably include the cases of Marble, of Malamud and Grosh, and of Wilder, but not of Tom and Richardson, to which reference has just been made. Lidz *et al.* describe a young man who was admitted to hospital five times in two years for fits and comas and who developed a mental state resembling pseudologia phantastica with speech defect, severe muscular atrophy and ataxia. Fifteen months after operation for islet-cell adenoma he recovered completely except for residual muscular atrophy. Black *et al.* and Smith and Cochran describe other striking recoveries in islet-cell cases and Jetter and Sheflen describe relatively mild neurone damage in a case which came to autopsy, but unusually marked gliosis and fibrosis had developed owing to prolonged survival. It is this extraordinary power of recovery which makes death a greater risk than permanent brain damage in islet-cell adenoma.

The position concerning the sequels of functioning islet-cell adenomata can be summed up as follows. If death or catastrophic damage to the brain can be avoided the potential for recovery is extraordinary; after a reasonable interval of time there is nothing between severe damage and none at all.

(The position concerning children is doubtful and is therefore noted in parenthesis. Wickes (1954) has put forward evidence suggesting that the foetus *in utero* is decreasingly susceptible to severe maternal hypoglycaemia up to the tenth week, thereafter there appears to be little danger to the child before birth. Jelliffe and Stuart (1954) have shown the extraordinary capacity of children to recover from severe hypoglycaemia if death is avoided, but there are many examples of mental defect produced by hypoglycaemia in children (Layne and Baker; Graham and Hartmann, 1934; Greenlees *et al.*, 1952) and this may be an expression of sensitivity to damage or the catastrophic dementia to which reference has been made showing improvement in resilient youth and the evidence I think favours the latter view.)

## MENTAL CHANGES IN SCHIZOPHRENIA

It should be noted that as opposed to the conditions before coma, one is dealing in the coma and its sequels with as near a standard situation for both islet-cell adenoma and schizophrenia as is possible. Time after time after such a crisis in the treatment of schizophrenia, there is a very dramatic, permanent, easily-observable change in the mental condition of the patient, always called an improvement, a word unknown in discussions on islet-cell adenoma cases. This improvement is directly related to the severity and duration of the irreversible coma: thus in sixteen cases reported by Wortis and Lambert (1939), two died, two showed no change after an average irreversible coma of eighteen hours, five were much improved after an average irreversible coma of thirty-two hours and a further week of stupor, and seven were "cured" after an average of forty-eight hours irreversible coma and four weeks of stupor. In other words, the greater the brain damage, the greater the improvement. Wortis and Lambert commented that if a safe method of producing irreversible coma could be discovered, a kind of reversible irreversible coma, it would increase the value of shock treatment. It is a change which has no connection with the gradual improvement which insulin coma often brings about or with the quiet deterioration which sometimes represents a failure of treatment. It is as if a picture of stormy uncertainty is suddenly replaced by a miraculous calm, a state of smiling peace in which it is easy to forget the broken boughs and the flattened flowers. The change is one in the condition of a schizophrenic patient and it can be said therefore that such a change could not be expected in normal patients and this is fully agreed. It is a change peculiar to schizophrenics.

As long ago as 1938 Kraulis was so impressed with the improvement in four out of five of his prolonged coma patients that he advocated pushing up the coma period to twelve hours, a procedure which proved too hazardous for general adoption. The same phenomenon was noted by Parfitt in 1937 and it has been stressed again by Revitch (1954) and Biskupski (1954). Almost uniformly the severity of the event has led to further treatment being abandoned so that, as Revitch has pointed out, there can be no doubt that the striking effect is an outcome of the prolonged coma. There is an abrupt production of sociability, even euphoria, a striking reduction of tension and hostility and an indifference to insane ideas where these persist, a picture, as Revitch again points out, which is very reminiscent of a post-leucotomy state in a schizophrenic. I would go further and say that without the possibility of palpating the skull the two conditions would be clinically indistinguishable. Even the first recovery from the critical condition, to the extent that life is no longer threatened, strongly resembles the immediate post-leucotomy state, with clouding, raised temperature and pulse rate, restlessness and incontinence giving way to drowsiness and apathy.

In my series of 290 cases there were 19 prolonged or irreversible comas of varying degrees of severity and roughly in proportion to the severity, the "prefrontal" picture was produced. It is difficult to draw a hard and fast line, but at least eight of the nineteen exhibited the phenomenon which is now being described, a sudden change of mental state which remains permanent in the sense that the residual palsies of the adenoma cases are permanent, over periods of months or years covering the observation. This peculiar group is confined to schizophrenia; it finds no counterpart in the islet-cell adenoma cases. In the same series of 290 cases there were no other notable sequelae other than five cases of persistent tingling and numbness in the fingers lasting for some months, similar to that described in one of Goodman's cases, occasional complaints of stiffness of the face which was usually more transient, and one permanent anosmia.

Putting aside the possible significance of an unusual sensitivity in schizophrenics under certain conditions, one is left with the fact that severe hypoglycaemic episodes have death, paralysis and dementia as their most prominent sequels in cases of islet-cell adenoma, whereas in schizophrenics these are comparatively almost absent; but a sudden and striking mental change, clinically for the better, is often seen as a sequel in about 3 per cent. of patients, a permanent change of personality of a kind unknown in normal people. (The condition might be suggested occasionally by such cases as Black *et al.*'s second case, the diabetic alcoholic reported by Bowen and Beck and one of Goodman's cases, but the picture is quickly lost in a steady recovery.) It does not matter how this is viewed, as a sensitivity of schizophrenics as compared with normals, or as a sudden shift in the disease itself, in either case an organic phenomenon peculiar to schizophrenia is evident.

There is, of course, no proof of its nature, but since the change produced is clinically identical with that produced by a prefrontal leucotomy in the same disease, it is permissible to speculate as to whether disease of the prefrontal lobes is important in schizophrenia. This is not a new idea, Schaffer and Miskolczy stated in 1938 that "The schizophrenic process destroys the most human parts of the brain", the frontal, inferior parietal and temporal lobes. Parfitt (1954) has marshalled evidence supporting the view that schizophrenia is incident chiefly in the frontal and temporal lobes and should be renamed phylogenetically and ontogenetically determined encephalopathy.

It might be asked whether this adds anything to the proposition that schizophrenics are often improved by prefrontal leucotomy, in which the improvement may be due to an opportunity for a somewhat simplified and fresh integration of function of the whole brain, and the answer is yes, because the change is brought about under circumstances which do not affect normal people in the same way and which suggest very strongly indeed that at certain stages of the schizophrenic process there is an extreme sensitivity to hypoglycaemia or to an excess of insulin.

No excuse is made for the absence of visible histopathology after the recent articles by Adrian (1954) and Murray (1954), although it might be pointed out parenthetically that Schaffer and Miskolczy based their opinion on microscopic examinations and claimed to have discovered lesions particularly in cortical layers 3 and 5, layers specifically mentioned by Malamud and Grosh.

The following two cases will serve better than further theorizing to indicate the effect of assuming that in fully developed schizophrenia a destructive process is at work in the frontal lobes and to a less extent in the temporal lobes.

*Case 1.* A highly intelligent girl who found little difficulty at first with her work as a librarian, but who at seventeen began to make errors and to suffer from periods of clouding, inexplicable impulsiveness and visual hallucinations which intrigued and frightened her and for which she sought an explanation. The disease from which she suffered was progressive, and at twenty-two she had thirty-two insulin comas in a mental hospital and sixty more a year later, each time with improvement. It is important to note that when she was able to seek guidance on visual hallucinations (and at this time her intelligence and ability as a poet was causing considerable interest), the patient survived without damage, in fact with apparent benefit, a total of ninety-two comas, a good many of them lasting a full hour after the corneal reflexes had disappeared. Two years later there was a further intensification of symptoms, the hallucinations became auditory and involved ideas of sex and guilt, she became crazily argumentative and easily excited and she was unable to maintain her employment. She was readmitted to hospital and on the very first occasion that she reached coma she suffered a delayed recovery and thereafter presented the picture of a severe physiological leucotomy, becoming quiet, bland and easy in manner. During the following two years she has fitted easily into her home, undertaken light household tasks and toyed with insignificant literature, and during the last month has got back to simplified library work. She has become careful of her appearance, is not hallucinated, has the peculiarity of sleeping very little without apparent discomfort, but she is a very inferior person compared with herself five years before. The events in this case become intelligible if one assumes that the disease process was at first mainly incident in the temporal lobes and that a state of frontal instability had developed when her last coma was induced.

The next case illustrates in more detail the physiological leucotomy which is being suggested.

*Case 2.* A young lady, now aged 29. Intelligent parents. Family eccentricity. One of three brothers had depression. Matriculated, good at games, kindergarten teaching from sixteen to nineteen before starting as a medical student. She gave this up after one year and was a nurse in training from twenty-one to twenty-five, completing her S.R.N. qualification and doing a further year as a staff nurse.

Schizophrenic symptoms began insidiously at twenty-four or earlier with increasing difficulty in coping with her work and withdrawal from friends and interests; she became perplexed, indecisive and unhappy, was inevitably slack at her job and later felt that the ward sister had a "down" on her, finally refusing to go on duty because people were talking about her and because references were being made to her in newspapers and magazines. At the same time she was assuming that a deep love affair existed between her and a houseman who did not know her very well.

She was admitted to hospital as a patient early in 1950 at the age of twenty-six, deluded and hallucinated and showing periods of restlessness, elation and noisiness. It proved difficult to induce coma but she had her third with 460 units on 27 April when the procedure for termination began after ten minutes, but the coma proved irreversible and she was never really conscious again for forty-eight hours and in the meantime was extremely near death. Three days after that she was still unresponsive, incontinent and being tube-fed, she did not speak until nine days after the injection of insulin.

During the remainder of 1950 she maintained a picture of bovine indifference, with tremendous loss of memory and concentration, she wrote simple letters as if her mother, who had died seven years before, was still alive and thought she had been in hospital for only a few days. She was quite unrousable to any sense of personal or communal responsibility, appeared colossally lazy and remained occasionally incontinent. She took reasonable care of her appearance and tended to moon after male patients.

Throughout 1951 and 1952 she improved very slowly, exhibited almost cyclothymic mood swings, varying from brightness and a superficial show of alertness to sulky aggression and resistiveness, at times doing simple work in a casual, unrelated way. Appropriate tears of bewilderment appeared occasionally. Tried at a local nursery she was reported as useful but not worth payment. Her nursing knowledge was considerably reduced but she was able to give useful if limited assistance as a ward help. In January, 1953 she did fifty-five out of sixty of Raven's progressive matrices in fifty minutes, which graded her "Intellectually Superior", her Conceptual Quotient was reported as 106 (over 90 is normal) and Mill Hill Vocabulary Grade 3+. "She was co-operative, cheerful and tackled the tests with interest and without fuss." She could play a good but casual game of hockey almost from the time of recovery from her coma. Eventually, early in 1954 she became a Deputy Assistant Matron in a preparatory school working under an understanding senior for sympathetic employers and she has moved into her second term successfully. Here is a girl who is now usefully active, has become pleasantly socialized, with a persisting weakness for assuming possession of a man, who goes out to films, plays games and does well with quite a variety of intelligence tests but who is yet pitifully different from what she once was. On close acquaintance she is found to be defective in original thought, has little insight into or interest in religious or ethical demands on herself as a person or in relation to her environment, the continuity of her personal memory is disorganized, she can only just manage to arrange her considerable knowledge well enough to become self-supporting under kindly and favourable conditions. Her ability to acquire new knowledge is considerably impaired.

As a description of a successful leucotomy this could hardly be bettered, so much so that one is tempted to speculate that the value of insulin coma treatment lies in the slow putting out of action of cells or circuits in functional disorder, that it helps to produce more smoothly a condition of stability in a disease which tends to produce its own leucotomy, and sometimes a very extensive leucotomy, that this is another example of the principle that damaged brain tissue is most susceptible to noxious agents, which was mentioned by Labbé and Boulin. This point is important, a physiological rather than an anatomical leucotomy represents a better procedure if it can be managed. Observe the complete absence of hallucinations in both cases cited.

## CONCLUSIONS

A comparison has been made of the effects and after-effects of severe hypoglycaemia due to islet-cell adenoma and of the same condition occurring in schizophrenia as a complication of insulin coma treatment.

The general picture, the clinical and chemical details of irreversible coma, the post-mortem findings and the fits show no certain difference, but death, paralysis and a dementia approaching mindlessness are tragically common in islet-cell adenoma and almost absent in schizophrenia, because of the safer conditions under which treatment takes place.

On the other hand, a peculiar, permanent post-irreversible coma state which is clinically an improvement and is indistinguishable from a "perfect" leucotomy occurs occasionally in schizophrenia. The irreversible coma which leads to this improvement usually develops with astonishing ease.

It is suggested that this is indicative of an organic peculiarity in schizophrenia.

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# PSYCHOENDOCRINOLOGY

By

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## PSYCHIATRISTS AND ENDOCRINOLOGY

THE last thirty years have witnessed the rise and fall of many theories and therapies on a supposed relationship between psychiatry and endocrinology, and perhaps the time is now ripe to weigh the evidence and attempt to draw at least tentative conclusions. A clear picture of an existing situation not only often leads to improved understanding but also to greater clarity of purpose.

Kraepelin, one of the founders of clinical psychiatry, expected endocrinology to provide the final solution in the pathogenesis and treatment of some psychiatric entities. Freud on many occasions expressed the hope that endocrinological investigations would supply the solution of many psychiatric problems. Bleuler (1954) has recently published a comprehensive book reviewing the endocrine investigations in psychiatry which have been published, but this admirable collection covers so many controversial and incomplete results that the author cannot even attempt to construct out of the chaos any concept about the actual role of endocrine function in the development of mental disease.

Mayer-Gross, Slater and Roth (1954) have recently published a book on clinical psychiatry which will certainly remain for many years to come a standard work on the symptomatology and diagnosis of mental disease. However, in spite of mentioning in the introductory notes that it is necessary to take account of biochemical investigations in modern psychiatry, endocrinology is only dealt with in a very cursory manner when considering the psychopathological phenomena occurring in the course of endocrine disease.

For various reasons the psychiatrists, of whom a majority had an entirely open mind about endocrinological psychiatry thirty years ago, have now sheered away from all discussion based on material which at first sight has no safe foundation.

First of all the great specialization of psychiatric research has led into various channels so divergent that the different investigators scarcely understand each other, and therefore cannot be expected to devote too much attention to each others work.

Then again many clinical psychiatrists have been dissuaded from further research by the frequent and often very rapid, though sometimes temporary, beneficial results obtained with E.C.T.

Some have embarked upon endocrinological experiment expecting a quick return from their efforts and, disappointed by their failure, have concluded that the endocrinological approach was altogether unsound.

So much of the experimental work has begun before satisfactory measuring methods had become available in endocrinology, and in any case the investigations were either carried out by psychiatrists who had no understanding of endocrinology and its methods, or by endocrinologists who had little or no experience with mental disease.

## ENDOCRINE FUNCTION AND PRECIPITATION OF MENTAL DISEASE

There can really be no doubt that hormones do have an influence on the mind. The obvious high incidence of mental disorder in adolescence, at post-partum and at the climacteric, three phases of endocrine instability, and the unmistakable action of thyroid hormone and cortisone on the mind, are enough in themselves to make it a safe deduction that the level of endogenous production of hormones exerts a powerful influence on the mental processes both under physiological and pathological conditions.

Progress in the analysis of psycho-endocrine interrelationships has unfortunately been retarded and for the most part only the extreme and clinically obvious cases of glandular disturbance have been studied from the psychopathological point of view. As endocrine diagnostic techniques become more accurate it will be possible to recognize earlier stages in the disturbances. For example, myxoedema, which is always associated with psychopathological disturbance, is rarely thought of as having developed by a continuously deteriorating thyroid function for a period of five to seven years before the final clinical diagnosis is made, and very few attempts have been made to correlate endocrine and psychiatric developments during this long phase. Indeed it may often be, and in the personal opinion of the author there is no doubt about it, that during this developmental phase such striking psychiatric diagnostic entities occur as to leave no occasion for considering the possibility of an underlying somatic disturbance.

The question is "where can the endocrine factor fit into the dominant theories in psychiatry?" Most psychiatrists agree about the importance of the pre-morbid personality pattern (mostly genetically determined). This is the factor deciding the quality of psychopathological manifestations that may be precipitated by various external or internal emergency situations.

The question, which, however, is only rarely asked, is why do some people who are able to withstand the same emergency situations for years ultimately break down, while others of quite similar personality make-up never break down mentally in spite of meeting even more severe emergency situations.

It is at this point that the somatic element must be introduced. Response to stress and emergency depends on the ability of the organism to maintain its biochemical equilibrium. When this equilibrium is sufficiently disturbed, whether permanently or only temporarily, the organism breaks down. Obviously this dis-equilibrium always affects the mind and the mood; and the direction of the mood changes, and whether the mental function remains within the range of normality or is sufficiently upset to result in a more or less severe psychopathological condition depends on the severity of the dis-equilibrium and the pre-morbid personality.

The probability of a break-down occurring under given stresses depends on the capacity of the various forces maintaining the biochemical equilibrium, and the width of the equilibrium which represents its adaptability varies considerably from individual to individual. One might compare it with an elastic rubber band, the quality of which determines how far it can be stretched. This is seen, for example, when after running for a short time one individual shows a decreased blood sugar, while another shows no change, or when an individual starts to show clinical symptoms during starvation or other stresses.

There is no doubt that the ductless glands are the main regulators of the biochemical equilibrium of the organism and the more we learn about their physiology the more we can see how even the simplest metabolic functions are finally dependent on the function of the endocrines and how the body equilibrium, which can ultimately be defined as a tendency to maintain a constancy in the chemical pattern of blood and tissue, is dependent on the co-operative effort of various ductless glands.

It is obvious that a decrease or an increase in the function of a ductless gland will have its repercussions on the width and stability of the biochemical equilibrium. Such a disturbance can, as a sequel, influence the work performance of another gland, so that once a disturbance of the biochemical equilibrium has started, a process of continuous deterioration has begun, which, if it is lasting, leads finally to a breakdown of the organism.

One of the mechanisms of adaptation of the organism to stress has been described by Selye in his general adaptation theory. This theory however, is only based on the pituitary anterior lobe-adrenal cortex axis, and certainly describes a very small part of all the forces at the disposal of the organism for maintaining its biochemical equilibrium, but it was a very useful beginning in regarding the adaptational efforts made by the organism. Similar adaptation theories can certainly also be made on the basis of the pituitary–thyroid axis (Badrick, Brimblecombe and Reiss, 1955).

To come back to the question which was asked previously, i.e. where the endocrine factor fits into the dominant theories in psychiatry, one can, on the basis of our present knowledge of endocrinology, say that the endocrine factor is wedged between the emergency situation and the pre-morbid personality pattern. The endocrine function determines, when an existing emergency situation will lead to the precipitation of psychopathologic phenomena in an

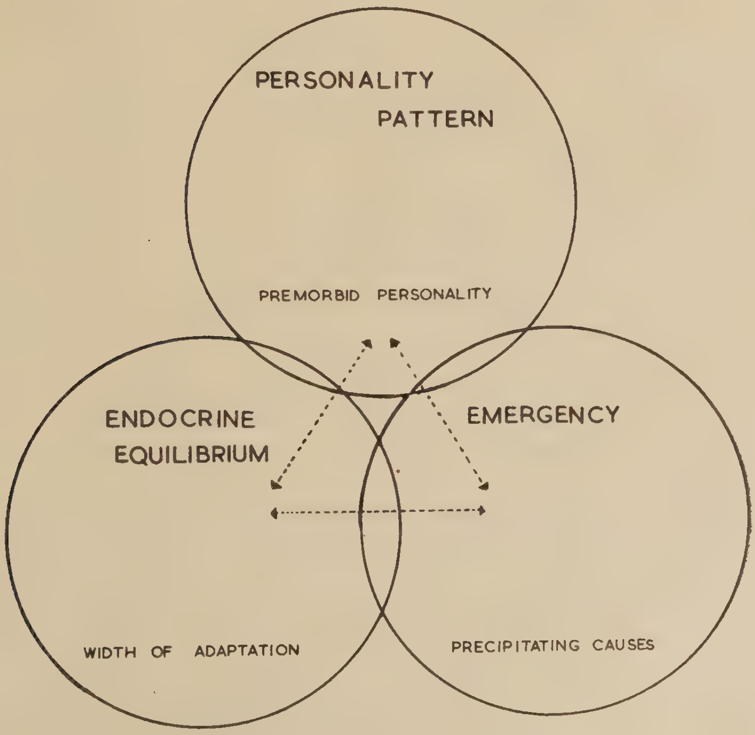

FIG. 1

individual of a certain personality pattern. A good working endocrine system is an efficient cushion between arising emergencies and the individual.

The diagram in Fig. 1 attempts to schematize the interrelation between personality pattern, emergency situation and endocrine equilibrium. These factors are set inside circles which intersect in order to emphasize the difficulty of separating the various elements. When specifying a primary role of any of these factors one should consider how easily the emergency situation produces endocrine disturbances, or how some endocrine disturbances occur more easily in certain personality patterns. Further, some emergency situations can become, in some endocrinologically or psychologically pre-disposed personality patterns, of much greater significance than in others.

### THE NEURO-ENDOCRINE INTERRELATION

The author has dealt repeatedly with the neuro-endocrine interrelationship in this journal (1939, 1944, 1954) and outlined its significance for changes in both brain and endocrine function. It was pointed out how emotions and psychic-trauma can, for instance, through a pathway over the hypothalamus, influence the pituitary to increase or decrease production of some trophic hormones, whereupon the quantitatively changed hormone output of the "target" gland acts back on the brain function, thus closing a vicious circle. It was pointed out how such a vicious circle can start by primary disturbance in any one of several levels; in the body periphery, peripheral ductless glands, pituitary anterior lobe, hypothalamus or higher brain centres. Such a disturbance taking place on any level must upset the whole neuro-endocrine equilibrium, starts a pathogenic cycle of events and often becomes progressively worse. Disturbances in the neuro-endocrine circle need not necessarily include the pituitary in their pathway in the first instance. They can, particularly under conditions of acute stress, start in the periphery by mobilization of large quantities of vaso-motor substances. It has been shown lately that certain endocrine reactions to stress take place at the same rate in hypophysectomized and normal control animals (Badrick, Brimblecombe and Reiss, 1955). The diagram in Fig. 2 illustrates the various components essential in psycho-neuro-endocrine equilibrium.

A clear realization of the neuro-endocrine circle can help us to a better understanding of the pathogenetic interplay between personality pattern, endocrine function and events precipitating mental disease. One realizes, for instance, that any lasting psychopathologic event must have an influence on the endocrine function. However, this change need not by any means be clinically recognizable since it is often much too new to express itself in a well-developed endocrinologic clinical disease entity which could be easily diagnosed.

The changes are mainly intermediate disturbances which should be detectable by investigation with laboratory methods. It is to be hoped that in future such sensitive and reliable methods will be developed which will enable us to detect any such intermediate disturbances inside the hormone equilibrium. At present only a method permitting the detection of intermediate thyroid disturbances is at the disposal of the author, yet even with this method alone a mental hospital population screened over three consecutive years showed thyroid deviations in about 30 per cent. of the patients (Reiss and Haigh, 1954).

The mental pre-disposition and nervous sensitivity of the individual is in many way decisive for the direction in which a neuro-endocrine vicious circle will develop. It is known, for instance, that Graves' disease develops mainly in predisposed persons. This state very often starts after a psychic trauma, which presumably produces more thyrotrophic hormone and this increased thyroid function; while in other persons the same trauma has no influence on the thyroid activity at all.

And again, it depends on the personality pattern how the increased production of thyroid hormone acts back on the brain. In some individuals there will be only slight effects on the brain function, or slightly increased nervous tension will be seen, while in others much more severe psycho-pathologic phenomena develop. Further, the same trauma or emergency situation that results in a disturbance of the thyroid activity in one person can produce in another individual menstrual disturbance instead with all its special psychologic consequences. The influence of worry on different personalities is very interesting. Some people will stop eating, others will eat much more than usual; some lose weight, others gain weight. This is another example of how an existing personality pattern can be decisive for the direction and the extent of a disturbance of the neuro-endocrine circle. The main decisive factors in this case being adrenal cortex and thyroid activity.

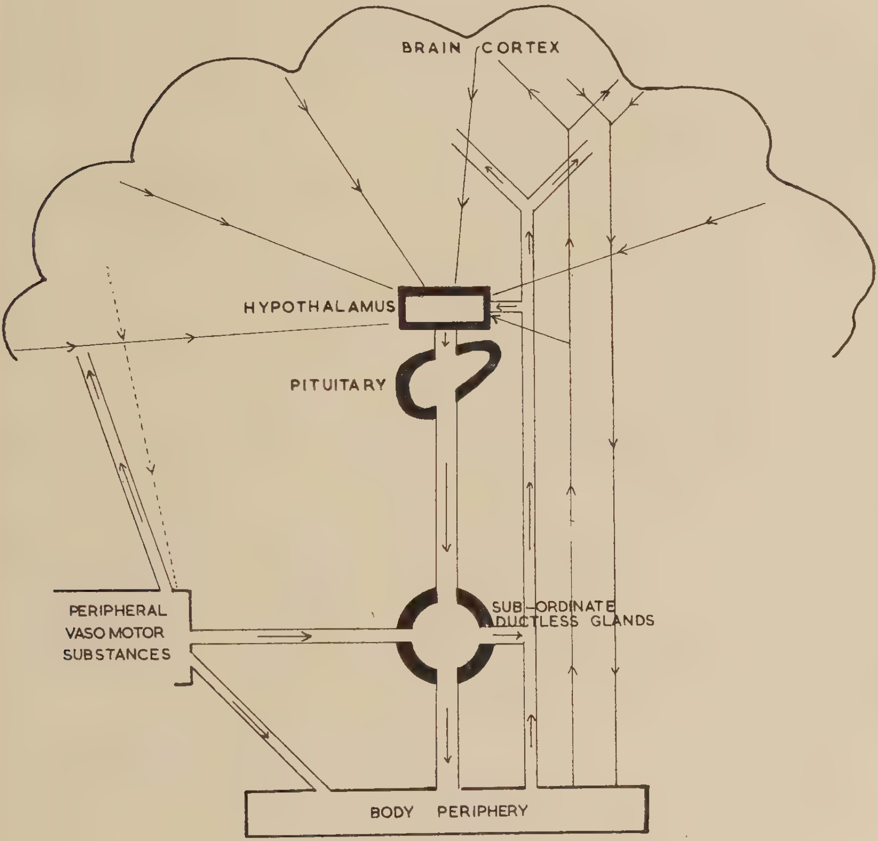

FIG. 2

Many other examples could be mentioned here to illustrate the inter-play between personality pattern and the neuro-endocrine circle, but only one will be mentioned here, namely that, according to M. Bleuler (1954), even brain lesions produce, in different personalities, different psychopathologic symptoms.

## PSYCHOPATHOLOGICAL MANIFESTATIONS IN ENDOCRINE DISEASE

Endocrine disease can, either alone or in combination with other emergencies cause psychological changes, which occasionally can reach pathologic dimensions. Quality and extent of the psychopathological changes depend apparently on the pre-morbid personality of the individual. A severe endocrine disturbance can be accompanied by a great variety of psychotic pictures or none at all. Bleuler has admirably and comprehensively reviewed the psychiatric symptomatology of the various endocrine disease entities. Surveying the whole material one finds, surprisingly, that there is but little difference between the psychopathology of hyper- and hypofunctional endocrine disease. Bleuler found, for example, no characteristic difference between the psychopathology accompanying Addison's or Cushing's disease.

This fact is very interesting in the light of our experiences (Reiss *et al.*, 1951) which show that identical psychiatrical diseases can be accompanied by different endocrine states. Under-function or over-function of the thyroid, for example, can be found in depressive states or in schizophrenia.

One must not forget that there are also many patients who, in spite of showing severe endocrine disease, do not show any psychopathological deviations. Emergency situations, however, which are easily overcome by most normal people, can lead to mental breakdown in endocrine patients. As already pointed out the psychopathological features in such patients can often be so predominant that the endocrinologic condition is easily overlooked, and one is surprised if relief of psychological or other stress does not immediately lead to improvement.

Bleuler comes to the conclusion that there are no specific psychological sequels of endocrine disturbance. He is of the opinion that all psychoses occurring during a severe acute disease fall into the frame of the acute exogenous reaction type as defined by Bonhoeffer. This assumption is also entirely in agreement with our own views, if one is permitted to circumscribe it as has been done above, namely, that quality and extent of the psychosis are determined by the personality pattern of the patient.

Psychopathologic disturbances seen in long lasting chronic, severe endocrine disease are likened by Bleuler to the mental disturbance seen in chronic diffuse brain lesions, the different symptoms being summarized under the collective title of the "amnestic psychosyndrome".

It is very regrettable that so few studies have been published of psychological investigations during the development of endocrinological disease. One may instance the frequently slow development of a state of adrenal cortex over-function when, at an early age, a child recovers from scarlet fever without any apparent complications, the adrenal cortex, however, remaining hypersensitive, particularly to the adequate trophic influences of the corticotrophic hormone, so that at the time of the adrenarche the adrenal cortex starts to grow and function abnormally, causing a multitude of somatic deviations, many of which are accompanied by various psychopathologic features.

Another example is the absence of investigations into the psychology of the occasionally slowly decreasing adrenal cortex function, a process terminating with Addison's disease. There are, however, some data already available about psychologic changes during the progress of thyroid under-function, culminating after a number of years in myxoedema.

These show that it is by no means always correct to assume retardation of the mental processes and sleepiness in thyroid under-function as it is so regularly described in the text-books of clinical endocrinology. Among the first complaints encountered in many patients in the initial states of hypothyroidism is the diminution of the receptor sensitivity. The threshold rises for hearing, seeing, tasting and smelling, and consequently the reaction time is also prolonged. The intelligence index, however, does not change at the same time, and the patients become aware of the fact that they are unable to make full use of their mental capacities. They feel that they are now less able to do their jobs—consequently conflict and mental stress situations are unavoidable.

The three pathogenetic factors mentioned above are then present, also the emergency situation and the disturbed hormone equilibrium which, according to the pre-morbid personality of the patient, can lead to a multitude of psychopathologic phenomena.

It is only a question of time until sufficiently exact investigation methods have been developed enabling us the better to detect intermediate endocrine disturbances which can be correlated with the accompanying psychologic and psychopathologic changes.

## Endocrinological Deviations in Psychiatric Disease and Their Changes During and After Empirical Treatment

A considerable drawback to progress in endocrinological psychiatry is the present classification system of psychiatric diseases. If a number of patients have even only one or two symptoms in common (such as ideas of persecution or hallucinations, etc.) it already suffices to shelve them diagnostically into one of the psychiatric disease entities. This happens even if the great part of the remaining psychological spectra of the various individuals in the rather enforced common group differ considerably.

The majority of clinical psychiatrists adhere strictly to this principle of classification and it is within the framework of these classifications of disease entities that the majority of all biochemical and endocrinological investigations have been carried out. The results were and still are much more controversial than the results of investigations carried out on patients belonging to a single nosological group of any other branch of medicine.

The "homogenous" psychiatric patient groups values of numerous biochemical blood and urine components were found to be either above or below or within the normal range, and in endocrinological investigation, normal, increased or decreased functions of the glands were found. The results were, of course, mostly evaluated statistically and one reached the obvious conclusion: "no statistically significant change."

The present dominant conclusion drawn in clinical psychiatry is to be found in the recent text-book by Mayer-Gross, Slater and Roth (p. 233) in their discussion about schizophrenia. "Thyroid, sex glands, adrenal cortex and pituitary have all been suspected as the primary site of the disturbance but with no conclusive evidence." No other conclusion can be expected if one considers the great lack of homogeneity in the physiological functions and pathophysiological disturbance in the investigated "homogenous" groups of schizophrenics.

Considering everything we know about the neuro-endocrine interrelationship and the decisive influence emotions and psychic trauma must play on the normal functioning of the ductless glands, it is probable that some disturbance in their function will exist in every serious neurotic or psychotic disturbance. If no concrete changes have been found so far in many of them, this conclusion is not invalidated considering how crude most of the endocrinologic investigation methods are at present. One can expect that with the progress in the development of these methods, many more endocrinological disturbances will be found in psychiatric patients.

We have indeed found (Reiss *et al.*, 1953, Reiss, 1953) many deviations in thyroid and adrenal cortex function in mental patients; in some of whom such changes were least expected since clinically they showed no sign of endocrine disease. The extent of the endocrine deviation varies from case to case, some being very far above or below the normal range, some having intermediate disturbances, indicating only a stage in the development of endocrine disease.

In the course of the investigations we also found an endocrine dysfunction which seems rather important in mental cases, namely, an insensitivity of the body periphery for certain hormones such as the thyroid hormone or adrenal cortex hormones (Reiss *et al.*, 1952). In such cases the B.M.R. is low in spite of undisturbed thyroid function, and even large doses of thyroid do not increase the B.M.R. Or, there is very little development of secondary sex characteristics in spite of the fact that normal or even increased amounts of 17-ketosteroids are being excreted.

However, no special endocrine disturbance was ever found in any of the disease entities, and vice versa. No significant correlation between the function of one single gland and any of the known psychiatric disease entities can therefore be claimed. However, if one looks at the changes in the total hormone equilibrium as such, and particularly at the equilibrium of the thyroid and adrenal cortex function, irrespective of the direction in which the function of the glands is changed, one finds a much closer correlation to disturbed mentation.

It seems that endocrinologic research in mental cases can only proceed with some hope of success if it is carried out on individual patients and the results carefully co-ordinated with psychopathologic symptoms, and later on statistically correlated in such a way that one of the factors is the result of the biochemical analysis and the other (if possibly measurable), a psychologic factor. It is feasible that in this way, in time to come, a system of classification will be found which takes into account not only a few psychologic criteria, but also body constitution and biochemical changes which may very well prove to be the cause of the psychopathologic deviations or the reason for their persistence.

Single biochemical investigations giving a static picture at a certain stage of the disease contribute comparatively little to the understanding of the pathognomonic significance of the biochemical change. Longitudinal investigations of the biochemical changes, repeated investigations throughout the duration of the disease and after recovery, and very careful chronological co-ordination of the changes in the mentation, permit more decisive conclusions about pathogenesis.

It has been found during the past few years that disturbed hormone equilibria often returns to normal when the mental state improves (Reiss, 1953). An extensive study was made (Reiss, 1954) in which the thyroid activity of over 400 psychiatric patients before and after treatment was investigated with a radioactive tracer method that permitted the detection of intermediate states of thyroid disturbance. A highly significant correlation was found between normal thyroid activity after treatment and mental improvement, and between thyroid activity outside the normal range and failure to improve. This correlation held good in all the disease entities investigated and was independent of the treatment applied (E.C.T., Coma Insulin Therapy, Modified Insulin Therapy and treatment with various hormones). Patients who showed spontaneous improvement after general hospital care and attention also showed a correlation between mental improvement and improvement of the thyroid activity. The changes in the thyroid activity which were found were regarded mainly as indicating more extensive alteration in the total hormone equilibrium of the patient.

It was particularly surprising to see that the same treatment, as for instance E.C.T., could be associated with increase of the thyroid activity in patients showing an initially decreased thyroid function and also with reduction of a previously increased activity towards the normal range. The explanation was given that E.C.T. does not influence the thyroid directly but interferes with the function of the pituitary anterior lobe and its production or release of the various atrophic hormones. All these hormones are known to be antagonistic amongst each other, thus, in some cases of thyroid under-function the endocrinologically relevant sequel of E.C.T. consists in an increased production of thyrotrophic hormone which might act either by stimulation of the thyroid or by suppression of thyroid antagonistic hormones; while in cases of increased thyroid activity secretion of more antagonists such as corticotrophic or gonadotrophic hormone result in the observed reduction of the thyroid activity. E.C.T. apparently influences the total hormone equilibrium. Changes in the thyroid activity indicate on this occasion only that a multitude of changes in the endocrine system take place.

It was pointed out that the action of other routine treatments on the hormone equilibrium as indicated by changes in the thyroid activity takes place in a way similar to the action of E.C.T., with the difference that other levels of the neuro-endocrine circle are acted upon.

## Expectation for a Rational Hormone Therapy in Psychiatry

It has been made clear above that hormone therapy cannot be used in mental disease simply according to the disease entity as classified at present.

At present one can certainly rule out any hope of ever finding a special hormone therapy for depression, schizophrenia, etc. It must be clear that all the older therapeutic attempts, in which special hormone treatments were recommended for a whole psychiatric disease entity (as for instance with thyroid hormone) and carried out on a large scale were bound to discredit hormone therapy in psychiatry.

The other danger for the introduction of a rational hormone therapy is the tendency to ask how many per cent. improvements were achieved. Taking the psychiatric disease entity as a basis for the calculation, such questions are completely unsuitable in the light of the facts explained above. It will never be possible to say, for instance, how many per cent. of acute female schizophrenic patients were cured with this particular treatment, but at the best only how many per cent. of those members of this patient group who showed, say, increased thyroid activity were cured by normalizing the latter. At the moment a description of a hormone treatment of even a very small number of patients who were successfully (or unsuccessfully) treated after careful hormone analysis is of much more value than a great statistical table about the success of some treatment based on a group containing members who are not physiologically homogeneous. Any hormone treatment in psychiatry can only be attempted on the basis of a preceding definition of the endocrine status of the patient.

It should finally be clear that our ideas of causation of the disease must be changed. If one succeeds in curing a patient, whose thyroid activity was found to be disturbed, by treating him from the thyroid angle, and mental normalization follows the regularization of the thyroid activity, that still does not mean that the disturbed thyroid activity was the cause for a disturbed mentation. We can think about the endocrine disturbance only as a part of a disturbed hormone equilibrium, and further, these endocrine changes are only inside the neuro-endocrine vicious circle (as explained above). Therefore, such improvements as are being seen after hormone therapy can only mean that the vicious circle was interrupted and do not give any indication of the place of the primary cause of the mental disturbance.

The therapeutic approach which can be made after the endocrine status is defined is in many instances still very much a research subject. It is comparatively easy in cases where the endocrine disturbance is so far developed that it can easily be clinically diagnosed, and where the clinical psychiatrist speaks of the occurrence of psychopathologic complications. That is the case in states now described as "myxoedema madness" or during Addison crises. The only precaution in the treatment of such cases is that it should not be started in a too precipitate fashion and only with small doses of the hormone required.

The therapeutic approach to intermediate disturbances which are mainly diagnosed on the basis of laboratory methods where only a few clinical symptoms, if any, are to be seen, is more difficult. One of the most important outcomes of the laboratory investigation of the hormone equilibrium (investigation of excretion of 17-ketosteroids and thyroid activity only) is the occasional ability to predict spontaneous mental improvement. A newly admitted patient occasionally shows, for instance, decreased 17-ketosteroid excretion and increased thyroid function. However, after a few days in a changed environment, the ketosteroid excretion starts to rise spontaneously, ultimately reaching a normal level, while the thyroid activity decreases simultaneously. In several of such cases we have correctly predicted spontaneous improvement.

Mental improvement can also occasionally be predicted in cases showing psychopathological features on admission or after completion of some routine treatment, but no outstanding disturbance in the thyroid–adrenal cortex equilibrium.

Study of the endocrinological changes seen after routine treatment with electroshock or during spontaneous improvement gave, in cases where spontaneous improvement could be excluded, the opportunity to try to imitate the action of E.C.T. by a less dramatic hormone treatment. For instance, in cases where the 17-ketosteroid excretion was low, the adrenal cortex responsitivity to A.C.T.H. disturbed, the thyroid activity high and no sign of a tendency to spontaneous change noticed, the hormone equilibrium could be restored by treatment with testosterone combined with small doses of oestrogen, this regularization being accompanied by mental recovery. In a case where both thyroid and adrenal cortex activity were very low, and where, therefore, an under-function of the anterior pituitary lobe had to be assumed, stimulation of the hypothalamico-pituitary system by implantation of testosterone led to the same result. By taking into consideration only 2 parameters of the hormone equilibrium, thyroid activity and adrenal cortex activity, a great variety of disturbances in the various patients can be found which should be dealt with individually if rational hormone therapy is to be introduced. In many cases the question of how to influence a disturbed hormone equilibrium is still very much a question of pure endocrinological research.

In cases of adrenal cortex under-function, for instance, under-production of a great number of various steroid hormones may be concerned which can, to some extent, be determined by chromatographic analysis, though this is still being developed. One of the outcomes of these investigations is a definition of a group of patients excreting decreased amounts of epi-dehydroandrosterone. They are mainly young, inadequate psychopathic types who occasionally overlap with a schizophrenic group.

Strauss *et al.* (1952) and Sands and Chamberlain (1952 and 1953), Zubiani and Caricchia (1953) have reported very encouraging results after treatment of such patients with epi-dehydroandrosterone (Diandrone).

Many satisfactory results of treatment of psychiatric patients with oestrone or testosterone have been reported. E. L. Margetts (1952) in particular recently reported beneficial results in a number of psychiatric conditions.

There is at present, however, a real danger that if such treatments are repeated without first establishing on the basis of hormone analysis an indication for the treatment of the individual patient, the application of sex hormones will become as discredited as previously the general application of thyroid therapy became. One of the simplest ways of testing the indication for treatment with sex hormones is an analysis of the prolan in the morning urine specimen. If the result is positive, which is quite usual in male and female climacteric conditions, treatment with sex hormones is certainly indicated, and can be continued as long as the prolan I reaction is positive. A low 17-ketosteroid excretion rate with or without accompanying positive prolan reaction can be an indication for the use of testosterone.

Some examples of the treatment of mental patients, after the thyroid activity has been investigated and found abnormal, have been published by Reiss *et al.* (1953) and Reiss (1954). Treatment of patients from the thyroid angle is by no means a simple matter. In mental patients, perhaps even more than in others, a decision must be made first as to whether the disturbance in the thyroid activity is primary or secondary to a pituitary disturbance. The possibility of peripheral over- or under-sensitivity to thyroid hormone has also to be taken into consideration (Reiss and Haigh, 1954).

## THE SIGNIFICANCE OF ENDOCRINOLOGIC PSYCHIATRY FOR CLINICAL ENDOCRINOLOGY

The endocrinologist is so dazzled by the enormous progress made in endocrinology during the last 25 years that he has tended to forget his original roots, which are the only guarantee for steady progress in endocrine therapy.

The chemical isolation of hormone compounds and the further development of hormone chemistry has, of course, opened a wide vista of possibilities in the further study of hormone chemistry and physiology, and last, but not least, for the use of the new methods as a basis for hormone therapy. However, at the same time this progress in the exact methodology has somehow made the chemist and biochemist forget that his work could not possibly have been started before exact biologic standardization methods made it possible to isolate, in ever-increasing purity, the hormone compounds he is investigating. The development of specific and exact biologic methods was never easy and could never have been begun if certain reliable physiologic actions of the hormones had not been demonstrated. The impetus to the later development came in the first instance from clinical observation of the endocrine disturbance.

We know that at present by no means all the hormones which play an important role in the organism have been discovered. There is, for instance, little doubt that the testosterone and other known androgens are not the essential hormone, nor are they the only endocrine product, of the male gonad. However, preoccupation with the presently much more easily obtained crystalline substance, and the absence of adequate biological standardization methods, discourages the research worker from further investigation of the endocrine function of the male gonad.

Endocrinologic psychiatry could supply the clinical endocrinologist with a mine of further information. The mental hospital contains a multitude of patients who are only just beginning to develop endocrine disturbances, and patients with intermediate disturbances where perhaps the only manifest clinical symptom consists of the mental deviation. The endocrinologist who at present deals mainly with fully developed endocrine-pathological symptoms has here the opportunity to learn something about causes and development of endocrine disease.

There is ample scope here for improvement in clinically useful and reliable hormone analytical methods, which permit the detection of borderline and intermediate stages of disease. But there is also an opportunity for reviewing and supplementing the methods of endocrine treatment. The basis of endocrine treatment was originally *substitution* therapy. Further progress in our knowledge of endocrine regulations—where the gland in the body starts to produce more hormones, under certain conditions—has opened up other possibilities for hormone therapy which may be called *supplementary* therapy.

One sees, for instance, that after severe burns when the adrenal cortex produces more corticoids, that it is useful to supplement this effort by the application of even further corticoids. Another instance, which fortunately occurs rarely at present, is the great effort made by the parathyroid during rickets, which in the end usually leads to tetany. This can be prevented by supplementation of this effort by parathyroid gland extracts.

However, particularly in emotional disturbance, one very often has to deal with hyperfunctional states, and their development. The endocrinologist bases his experiences in hyperfunctional states mainly on *surgical* methods. Methods dealing only with the conservative inhibition of an increased functional state are few. Work concerning the *inhibition* therapy is proceeding only in connection with thyroid hyperfunction. There are, however, many states of hyperfunction in other glands, in particular the adrenal cortex, where the hyperfunctional states have intermediate stages between the normal state and adrenal cortex adenoma. Such disturbances are certainly not clinically irrelevant, but next to nothing has been done to circumscribe them clinically.

Finally, clinical endocrinologic psychiatry gives the endocrinologist the opportunity to study spontaneous changes in glandular function. He can see how, for example, hyperfunctional states of the thyroid can occasionally improve in a comparatively short time after the patient's entry into hospital, in other words, by change of environment. There is still open to the endocrinologist a wide field for therapy by *environmental* and other unspecific factors.

We have tried in this paper to show that there is still a wide field for investigation of minor and unclassified endocrine variations, and that the application of the detection of these deviations to the treatment of mental disease, irrespective of the clinical psychiatric diagnostic labels, can often result in improvement in mental health.

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# A PROPHYLACTIC APPROACH TO CHILD PSYCHIATRY

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It has long seemed apparent to workers in the child guidance field that many of their patients show evidence of longstanding emotional disturbance; either the symptoms now complained of have been present for many years, or there has been a history of symptoms earlier on which have disappeared only to be replaced by the existing ones. Some of these patients whose present condition may be almost intractable, might have been helped had they been treated at an earlier date, while recent work by Bowlby (1951) and others has emphasized how important are security and satisfactory emotional relationships in the early years for the establishment of a stable personality. Thus it appears that any prophylactic approach, aimed at reducing the incidence of emotional disturbance in older children, and it is hoped ultimately in adults, may need to be made very early in life.

Little has been published, apart from accounts of individual patients, of work on any series of very young children who were psychiatrically disturbed, particularly from a prophylactic point of view. Joseph (1948) has described some of the patients she has seen in a child guidance clinic attached to a child welfare centre, and Gillespie (1954) has compared the symptomatology of a series of pre-school children treated at Infant Welfare Centres with the pre-school histories of older children treated in a child guidance clinic. She points out that the type of problem dealt with in the under-fives was seen in a high proportion of the earlier histories of those who needed treatment at a later age. The importance of early treatment for parents in the prevention of serious disturbance in the children has been emphasized by Fries (1946) by Jacobs (1949) and on a community scale by Caplan (1951). His experience in Infant Welfare Centres in Israel over a number of years has led him to concentrate on the treatment of cases where abnormal symptoms were not yet manifest, but where pathogenic relationships of the parents to the child were such that he felt that emotional difficulties in the child might later develop. In this country such a prophylactic approach is relatively unexplored, although the possibility of preventing mental ill health in children is one which has interested public health authorities for some time.

## Psychiatric Findings in School-age and Pre-school Children

That psychiatric disturbance seen in the ordinary run of child guidance patients may be longstanding is well illustrated by the early histories of 100 children of school age (5 to 15 years) who have attended Brixton Child Guidance Unit. These case histories were selected only to the extent that children who had been in institutions from infancy were excluded, or in whom for some reason details of infancy and early childhood were unobtainable. It was found that 39 per cent. of these patients have shown symptoms indicative of emotional disturbance in their first year of life and 74 per cent. of them in the first five years of life. Such symptoms covered the whole range of childhood behaviour and they included, for example, difficulties in feeding and weaning, excessive crying in infancy, undue dependence on the mother, disturbance of sleep, excretory dysfunction, and most common of all, manifestations of aggression.

Such common findings at so young an age again closely followed Gillespie's (1954) findings and point to the importance of psychiatric treatment early on; and a child guidance clinic, which serves a relatively small local area and which maintains a close contact with agencies responsible for pre-school children, will allow very young children in an early stage of psychiatric disturbance to be referred for treatment. Thus, it was also possible to examine a series of 50 pre-school children treated at Brixton child guidance unit over the same period, and to compare them with the older group. The age range in this series was 18 weeks to 4½ years; 29 (58 per cent.) were boys and 21 (42 per cent.) girls. The majority (68 per cent.) were referred by local child welfare clinics, a further 24 per cent. by general practitioners, and the remaining 8 per cent. by other sources.

It was characteristic of these very young children that almost every mother complained of a large number of symptoms at the initial interview, and in the course of ordinary history taking revealed a number more. This is shown in Table I, and it implied that without exception these children showed evidence of disturbance in most aspects of their behaviour and they again paralleled Gillespie's findings (1954).

TABLE I

*Symptoms Found in 50 Pre-School Children (Under Age of 5)*

| | Symptoms Spontaneously Complained of by Mother in: (Children) | Other Symptoms Elicited in: (Children) | Total | Per cent. |
|---|---|---|---|---|
| Aggressive manifestations .. | 26 | 14 | 40 | 80 |
| Sleeping difficulties .. .. | 15 | 25 | 40 | 80 |
| Enuresis .. .. .. .. | 15 | 6 | 21 | 42 |
| Feeding difficulties .. .. | 14 | 16 | 30 | 60 |
| Overdependence and clinging to the mother .. .. .. | 5 | 20 | 25 | 50 |
| Encopresis .. .. .. .. | 3 | 3 | 6 | 12 |
| Speech difficulties .. .. .. | 3 | 1 | 4 | 8 |
| Masturbation .. .. .. | 2 | 3 | 5 | 10 |
| Fears .. .. .. .. | 2 | 14 | 16 | 32 |
| Eczema .. .. .. .. | 2 | — | 2 | 4 |
| Backwardness in development .. | 1 | — | 1 | 2 |
| Asthma .. .. .. .. | 1 | — | 1 | 2 |
| Overt jealousy of siblings .. .. | 1 | — | 1 | 2 |
| Regressive behaviour .. .. | 1 | — | 1 | 2 |
| Tics .. .. .. .. .. | — | 1 | 1 | 2 |
| Attention-seeking behaviour .. | — | 3 | 3 | 6 |
| Wandering .. .. .. .. | — | 2 | 2 | 4 |

Seventy per cent. of these children had been considered "difficult" for one reason or another during the first year of life, a marked contrast to the older child of whom it was often recalled that he "could not have been a more perfect baby". It is not suggested that older children with psychiatric disturbance did not show earlier difficulties, as the findings in the older group have shown that this was not the case; it is that mothers tend specifically not to recall and so not to complain of earlier problems. Such a repression is commonly seen in mothers who appear to find it impossible to accept their role in the production of the child's symptoms and so may concentrate on a relatively unimportant symptom which, they feel, can be attributed to external causes.

Further comparison of the clinical findings between the pre-school children and those referred at an older age showed more difficulties with breast feeding in the former. Fifty per cent. of the pre-school children had not been breast fed at all as opposed to 30 per cent. of the older group; a further 10 per cent. in each group had been weaned because of difficulties during the first three months. The causes for these failures to breast feed could not be accurately assessed in either age group. Most of the mothers adduced physical reasons, and very few were willing or able to talk about their emotional reactions to feeding except in conventional terms. From subsequent knowledge of the mothers' personalities, however, it seems likely that for a considerable number it had been a very disturbing experience.

The 50 mothers of the pre-school children formed an interesting group. Twenty-four were considered frankly neurotic, 20 more were over-anxious or mildly unstable and one was a certified defective. Of the 5 considered to be stable people, 2 were mothers of defective children. They all showed relatively more anxiety than the corresponding group of mothers of school age children and, it seemed, at this much earlier stage, more awareness of the unsatisfactory nature of the mother–child relationship. They did not seem to enjoy their children and felt they ought to do so, but had, as a whole, much more insight into their own part in the production of the difficulties. This may be because the mother and child, at this early stage, approach more to a symbiotic existence and the mother is perforce much more involved in the child's emotional development than during the latency period. This, not unnaturally, sometimes led to special difficulties in treatment, as the mother who finds that her child, who she says can never be left with strangers is, after a short time, quite happy for 30 to 40 minutes with a therapist may exhibit much jealousy and hostility as her own insecurity mounts.

Forty-one pre-school children were given systematic treatment; 3 further patients, including 2 children who were mentally defective, did not require it; 6 further mothers refused treatment. The immediate results are shown in Table II and compared with the immediate results in the series of 100 older children.

TABLE II

*Immediate Result of Treatment in Percentages*

| | 50 Children Aged under 5 | | 100 Children Aged 5 to 15 |
|---|---|---|---|
| | Per cent. | Patients | Per cent. |
| Symptom free .. .. .. | 32 | (16) | 23 |
| Improved .. .. .. | 40 | (20) | 34 |
| No change .. .. .. | 24 | (12) | 38 |
| Worse .. .. .. .. | 4 | ( 2) | 5 |
| | 100 | (50) | 100 |

The most likely reason for these more favourable immediate results is the young age of the child. The position in regard to development is still fluid, and it is hoped that by early treatment the child may be helped through critical phases in his development, and the mother enabled to give him security at a time when it is of such vital importance. There seem, however, to have been contributory factors. The parents of these young children tended themselves to be younger than the parents of older children under treatment, and therefore more often amenable to psychiatric guidance. Indeed, they nearly all had sought help of some kind from someone they considered an authority, whether general practitioner or welfare clinic. They may not at first have been anxious for psychiatric help, and a few found it very difficult to accept in the first place, but the group as a whole was in marked contrast to the parents of the school age referrals. Many of this latter group did not even consider the child a problem, or were unwilling to accept any responsibility for his behaviour and only brought the child to the clinic as a result of considerable pressure from some interested social agency. This distinction is further emphasized by comparing the numbers whose cases had to be closed as "unco-operative". These amounted to 26 per cent. of the group of pre-school children compared with 34 per cent. of the group of older children. They included a number who at once failed to attend; but if these are excluded, the comparative figures are 14 per cent. of the pre-school children and 29 per cent. of the older children.

The main cause of patients failing to attend or for breaking off treatment, and especially in the older age group, was that the parents appeared to have been over-persuaded by social agencies to attend the clinic, but still failed to recognize the need for psychiatric help. Other mothers found that psychiatric treatment meant the reawakening of disturbing factors in their lives and felt unable to face these so that treatment was broken off. A further difference between the two groups was that they tended to belong to rather different social groups. The two child welfare clinics from which a large number of the young children were referred, are in areas which contain a relatively high proportion of lower middle class families and a relatively small number of the near problem families who formed a significant proportion of the older referrals. It was also easier to contact the fathers of the younger children. Social factors were again important over this, but it may also have been because the marriage, though often unhappy, was like the child's problem, still in its relatively early stages, and had not crystallized into one of the hopeless marriages which were more likely to exist between the parents of nine or ten year olds.

The fact that psychiatric treatment of emotional disturbance in children in the pre-school phase on the whole led to encouraging results compared with that in older children, and also needed to be continued for a relatively shorter time, did not necessarily obviate the need for further help in the future. Amongst the present series it seemed clear that many of the children (and mothers) might need help at intervals throughout childhood, and it can be envisaged that such patients may need to keep contact with the child guidance clinic over a number of years with perhaps periods of more intensive treatment from time to time. Some mothers, for instance, who found it difficult to deal with the child's normal expression of aggression may well find in due course that a relatively minor degree of sibling jealousy is hard to accept; both mother and child may need help to work through this when it arises.

## A Psychiatric Service in Maternity and Child Welfare Centres

Arising out of the encouraging clinical experiences illustrated by this series of pre-school children, it was decided, with the co-operation of the

Divisional Medical Officers and the clinics' staff concerned, that more might be achieved if a psychiatrist from the Brixton Child Guidance Unit attended regularly at one or more of the local Maternity and Child Welfare Centres; it seemed possible that there might be a further group of children attending there who were in a very early stage of psychiatric disturbance. It also seemed possible that the anxious and insecure mother who would not readily accept referral to a child guidance clinic, might accept psychiatric help in the child welfare centre itself, with the reassurance of familiar surroundings and personnel. This was found to be the case, so that three centres were visited more or less regularly over a period of twenty months. At first fortnightly visits were paid and on the whole this routine was continued in two centres, though at times the number of referrals lessened and attendance was cut down to once in every four to six weeks. In the third centre, regular visits were discontinued after a short time as it seemed more satisfactory for the doctor in charge of this centre to refer patients direct to the child guidance unit.

In the other two centres, where a regular psychiatric service continued, procedure varied with increasing experience. The medical officer in charge of the centre was normally responsible for referring patients for psychiatric assessment, when symptoms in the child or mother appeared to warrant it. A few were so referred at once while attending for routine examination, but the majority were asked to come later for a special examination. The fact that this was a psychiatric examination was not stressed. In addition, in one centre it was possible to "sit in" during the routine examination of infants, and so to explore with the doctor and health visitors the psychiatric aspects of management, or to facilitate the discovery of psychiatric disturbance when present. This was found to be most helpful and instructive both to the psychiatrist and to the centre personnel; it would probably have been even more helpful in a toddlers clinic (i.e. for children of 14 months upwards), but unfortunately lack of time prevented this.

A total of 34 cases were interviewed in these centres in 20 months. A further 3 patients refused the interview. The type of problem met varied a little with the clinic and ranged from the depressed and anxious mother of a very young baby who was concerned about her failure to breast feed, to the unstable and immature mother of the aggressive toddler who in no way differed from the ordinary run of pre-school referrals seen in the child guidance clinic. In one centre, where the doctor was particularly interested in the psychiatric symptoms to be seen in young children, any patients referred for psychiatric assessment tended to show overt disturbance in the child; in another centre, where most of the referrals were made on the instigation of the health visitor, the mothers tended to show more obvious inadequacy in dealing with normal stages of development in the child. However, in 6 of the cases seen, the mothers were found to be depressed, the children being relatively healthy; 4 of them could be classified as puerperal depression, of which 3 were clearing spontaneously. The other 2 mothers were severely neurotic people, one of whom had received prolonged psychotherapy in the past while the other was later referred to an adult psychiatric clinic for treatment.

After the preliminary assessment in these 34 cases, 12 were transferred to Brixton Child Guidance Unit, either because it was felt that the child needed such further investigations as psychological testing, or because the situation warranted prolonged treatment which could not be given in the child welfare centre for reasons of time and space. Of these 12 patients, 6 were taken on for formal psychiatric treatment on a weekly basis; the psychiatric social worker then dealt with the mother while the psychiatrist continued to treat the child. A further child was proved to be of backward intelligence; no gross emotional problem was found and in due course a recommendation for ascertainment as Educationally Sub-normal was made. In 2 more patients, it was subsequently considered that no active treatment was necessary, but they were followed up at regular intervals in the child guidance unit and help could have thus been given at any time should it have been needed. In 2 other patients active treatment was advocated but in each case the mother refused it. In the last case, the mother later had to be referred elsewhere for psychiatric treatment in her own right. A further 3 patients were offered child guidance treatment but refused the initial appointment at the clinic.

Of the remaining 19 patients 9 were given supportive treatment in the child welfare centre itself for periods of between one and five months. These were all cases of anxious mothers of first children, who were either young and immature or elderly and rigid and for whom the advent of a child was a most disturbing occurrence. They were reacting with either over-anxiety and in most cases some depression to the normal difficulties associated with the child's increasing demands, and were helped by a relatively superficial discussion of their problems. In most, simple discussion of the management of a situation led to a change in the mother's handling with consequent improvement in the child. These mothers may need further support at intervals during the child's development, but it is probable that with increasing awareness by the health visitors concerned of the emotional factors operating in these cases, much of the support can be obtained from them. Two other mothers were offered similar supportive treatment, but did not avail themselves of it. Two more cases were referred elsewhere for treatment: one child with asthma was found to have no gross psychiatric symptoms and required physical investigation, and in another the mother was found to have a severe puerperal depression and was admitted to a mental hospital. The remaining 6 cases were not treated further after the preliminary interview; 4 because the symptoms complained of appeared to be clearing spontaneously, and in the other 2 it was the fathers who were seen but who were found to refuse any help that could be offered them. These fathers were both referred by the health visitors who had found them anxious, demanding and difficult people and did not know how to help them. Both were most unstable, one it transpired had made a suicidal attempt and later regularly attended a psychiatric clinic. They both came for interview with a long series of accusations against their wives and had invoked the help of numerous social agencies in the past. They neither expected nor would accept any help, but it reassured the health visitors to feel that they had been seen by someone with psychiatric experience.

## DISCUSSION

It is clear, judging by the experience gained in attending these child welfare centres, that useful psychiatric work can be done there, although much will depend on the building up of a co-operative relationship between the visiting psychiatrist and the clinic personnel. It was not possible, however, to assess what proportion of the population attending child welfare centres was emotionally disturbed, as only a very small fraction of the total was psychiatrically examined. For instance, the average attendance in any one infant clinic may be 40 to 50 a week, of which perhaps 15 may be seen by the medical officer. In a toddler clinic the attendance is approximately 15 to 20 patients a week. It seems probable that the small number of 35 patients in 20 months who were referred for psychiatric examination by no means represented the total number who could have been so benefited.

The problem of deciding which patients were essentially "normal" in spite perhaps of minor upsets, and which should be regarded as psychiatrically disturbed, is one which has preoccupied the child welfare centre staffs. A psychiatrist, on the other hand, needs the experience of working with a large number of mothers and young children to appreciate how wide is the range of so-called "normal" childhood behaviour and how almost universal is some degree of anxiety on the part of the young mother of a first baby. Thus, continued contact by the psychiatrist with a child welfare centre and discussion of patients with the centre staff, has allowed clinical experience on these matters to be built up by the psychiatrist. At the same time, it has led to a greater awareness by the staff of emotional disorders in their patients. At first, much of the psychiatrist's work consisted of trying to pick out mothers and children in the early stage of psychiatric disturbance which, if overlooked, might have led to illness of greater severity. Increased awareness and experience by the centre staff in these matters might lead, however, to their undertaking such selection themselves. Such patients, if the centre staff felt they could not handle them themselves, could then be referred to the psychiatrist on the spot or to a local psychiatric clinic. The psychiatrist, apart from acting in a consultant capacity, would then be more free for instance to investigate the possibilities of mental health work with the centre patients.

It is a matter of speculation how far the doctor or health visitors on the staff of a child welfare centre can take psychiatric responsibilities. They are in a unique position in relation to mothers, and already do valuable work in physical supervision, education and in supporting anxious mothers. They have, however, no special training at present in these matters; they would need time to be set aside for such work, and their interests and the suitability of their personal qualities would be important factors. However, 11 of these 35 patients seen in these child welfare centres might have been successfully handled by a member of the centre's staff with the necessary skill, although the wide range and varying seriousness of the psychiatric problems met in these patients as a whole, stressed the need for skilled diagnosis and overall psychiatric supervision. How such training should be imparted would need careful consideration, but the shortage of psychiatric personnel precludes the sort of work outlined except in special circumstances.

In conclusion, "prophylactic" work such as described here, can only reach a limited number of mothers. Not all amongst regular attenders at the child welfare centres were found to be suitable patients for such an approach. Again, varying perhaps with the district, there are many mothers who do not come to child welfare centres, and amongst these are the less stable and the less intelligent mothers and also the mothers of problem families. It is probable that these latter form later on the hard core of perhaps intractable patients so often referred to child guidance clinics.

## SUMMARY

The importance of dealing with children in an early stage of disturbance is emphasized by the examination of the early symptomatic history of 100 school age children referred to Brixton Child Guidance Unit. Fifty cases of pre-school children treated at Brixton are also examined with the results of treatment. Clinical work in Maternity and Child Welfare Centres is described. Established cases of early disturbance have been recognized and treated there and educative work with centre staffs carried out. A possible extension of prophylactic work is described.

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# THE CONCEPT OF RESPONSIBILITY

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> "No man is an iland, intire of itselfe; every man is a peece of the Continent, a part of the Maine; if a Clod bee washed away by the Sea, Europe is the lesse, as well as if a Promontorie were, as well as if a Mannor of thy friends or of thine owne were: any mans death diminishes me, because I am involved in Mankinde. And therefore never send to know for whom the bell tolls; it tolls for thee."—John Donne.

## Introduction

If "responsibility" has any useful meaning, it is in the sense that we are all responsible for one another. As any man's death diminishes me, so any man's defection diminishes me.

The concept of criminal responsibility in particular (which does not differ in substance from any other kind of responsibility) has long bothered lawyers and psychiatrists who, in their wrangling over this issue, never seem to come to grips with the essence of the problem. This is perhaps to be understood in view of the fact that their training does not encompass much, if anything, in the way of fundamental psychological principles, scientific attitude or philosophical approach; and this matter of responsibility is properly one for the psychologist or philosopher who has had such training (and not all of them have) to treat. The untutored layman frequently gets away with a brash voicing of his opinions on psychology as a result of much psychological terminology being in common currency, although with different meaning, and of every man regarding himself as a psychologist, especially where he is ego-involved. The psychiatrist or lawyer often gets away with his views on psychological and philosophical topics for similar reasons, but more weight is apt to be attached to these opinions by virtue of the prestige enjoyed by his profession. This tendency is nicely illustrated in a recent paper on responsibility (Lowrey, 1953) where the writer disarmingly tells us that the subject matter lies in "conceptual fields quite different" from those which ordinarily concern him and that his training has been in anatomy and pathology. A logician writing about the operative procedures employed in temporal lobectomy would be no more misguided an excursion. This writer cavils at "the roundabout fashion in which determinism [as defined by Webster's Dictionary] may maintain the idea of a free will" but goes on, tripping through non-sequiturs, self-contradictions, a confusion of logical categories and a lack of appreciation of semantics, to embrace both of these himself, commenting: "To find good examples to prove [*sic*] the co-existence of determinism and freedom of choice . . . has not been easy." At least he does put a finger on the point that determinism eliminates responsibility and focusses attention on the paradox that: "If we, as psychiatrists, regard recidivists as being in greater or lesser degree mentally sick, even though not insane or feeble-minded, then we must stand for a concept of limited or qualified responsibility and believe that the framework of determinism is pathologically altered so that freedom of choice is impaired."

Turning from notions of diseased determinism to views of the Royal

Commission on capital punishment, we find that (Wingersky, 1954): "Despite frequency of investigations in these areas and advancement of medical science to its present status, these investigators were still driven back to the recognition that a moral question confronted them whenever they touched the question of responsibility." Yet the Commissioners announced their desire to avoid "philosophical arguments which have led to barren controversy in the past". According to Wingersky: "Whether the current doctrine of responsibility reflects both 'contemporary moral standards' and the latest medical knowledge is the core in the struggle for an opinion on the cardinal issue, viz. retention or abrogation of the M'Naghten Rules." He also quotes Turner that "the courts are not concerned with insanity as such but with criminal responsibility". It is difficult to see how any amount of medical knowledge could in the slightest affect such a problem. The reference to "contemporary moral standards" (which have not been clearly defined or systematically assessed) is manifestly a sop to public opinion, which it would be immoral and irresponsible of any scientist to let influence his conclusions. Whether the Commissioners like it or not, the problem is of the same kind as that discussed in a broadcast series a few years ago under the heading of "The Physical Basis of Mind" (Laslett, 1950), of which Ayer remarked that it was not a scientific but a philosophical problem. It was striking that all of the very distinguished scientists who spoke in this series, with one exception (as was pointed out at the time by Ryle), automatically posed the problem in terms of body–mind dualism (like Ryle's peasants who, seeing an engine for the first time, thought that there must be a ghost-horse inside it)—which was, of course, implied in the very title. Zuckerman it was who said: "If mind is conceived of as something which interacts with body—or as some parallel manifestation to body—the scientist may be misled into trying to solve problems which may prove unreal."

The functions attributed to modern philosophy by Drever (1949) are clarifying concepts and integrating the findings of the various sciences: the first of these concerns us, the second is the more difficult since few can be in a position to know enough about the different sciences even to attempt their integration. Regarding the former, Drever says: "The scientist can examine his own basic concepts, of course, but if he does he is philosophizing, and experience shows that he will philosophize less effectively than those who have been trained to do the job. In particular, our basic concepts—or ways of talking—about human beings are in need of clarification and refinement. In this field, above all others, the scientist must look to the philosopher, forgetting, if he can, that from some philosophers, notably Descartes, he has already had some very misleading suggestions." The (largely Cartesian) legacy of "mind *and* body", states Sinclair (1951), "has been given up by many and perhaps most philosophers, psychologists, and biologists, and by many theologians, but it is still held by other workers in these fields and presumably by most plain men". He goes on to say: "The common-sense theory that there are minds and that there are bodies may be convenient to hold for certain limited purposes, but it is, strictly, untenable, and therefore in any philosophical, psychological, ethical, theological or other discussion of fundamental issues, references to the mind and to the body as distinguished one from the other in the common-sense way ought not to appear . . ." It is from a background of this dualism, together with the archaic faculty psychology recognized in legal discussion or the outmoded Freudo-McDougallian psychology so firmly entrenched in psychiatric circles, that the present-day concepts of responsibility have arisen.

Misunderstanding of the nature of the problem is well illustrated in the correspondence (particularly that of 16 October) ensuing upon the publication of Slater's (1954) article on "The M'Naghten Rules and Modern Concepts of Responsibility"; even so obvious a statement as "No theory of mental medicine could develop without the working hypothesis of determinism" is an alien thought to some of these writers and frequently fires off an emotional charge. To err is philosophical, as well as human, however. Some philosophers do not appear to have negotiated their way past the clicking billiard balls of Hume, or the idea that determinism is somehow tied to the particular laws of classical mechanics instead of being a principle basic to all the sciences (cf. Bergmann, 1951)—and not, we might add, a mere assumption, for it has the whole body of scientific knowledge to support it. Smith (1954) writes in terms of a faculty psychology divorced from modern psychological knowledge relevant to his subject and unappreciative of the status and use of words and theoretical constructs; apparently unable to escape a hypostatization of concepts such as "desires" and other "forces", he ends up in the same philosophical naïvety as Lowrey (1953) and in agreement with Campbell (1951) that: "Action, although free, will be limited to those courses of action which the interests, guided by the intelligence, of the agent suggest to him as possible modes of self-satisfaction", and that "freedom exists only within this prescribed area".

Another facet of this matter of appropriateness is strangely perceived by East (1949), who asserts that "some psychologists who have no medical qualifications and no training in psychiatry are too ready to make a diagnosis concerning the mental condition of offenders they examine", and that since the "number of non-medical psychologists seems likely to increase, and their divergent views are likely to confuse juries if they are expounded in the criminal courts", these would best be served by "refusing to accept the opinions of non-medical psychologists and psychotherapists". He also states: "It is important to check the natural tendency to over-interpret criminal behaviour in terms of mental abnormalities which are found in non-criminal cases." In other words, assuming that criminals include both psychologically normal and psychologically abnormal persons, psychiatrists are entitled to pass opinions on both the normal and the abnormal while psychologists are not entitled to pass opinions on either. It is not evident which species East was criticizing: when this essay was written, both non-medical psychotherapists and clinical psychologists were few and far between, their appearance in the courts (if indeed they were admitted as expert witnesses) even fewer and farther between. As to the divergence of views, it could be no more than that between different psychiatrists.

## Ideas About Responsibility

In the ancient Common Law, the function of the law was to regulate the compensation to be paid for harm done rather than to punish the doer and mental processes were taken into account very little if at all. Nowadays, in some crimes it has only to be established that the accused was physically responsible for the crime, i.e. that he has brought about a state of things which the law prohibits (*actus reus*); in others, it has also to be established that a certain culpable state of mind must have inspired or accompanied the conduct of the accused (*mens rea*), allowance being made for the subjective element of excuse in some cases. When this subjective element was introduced, under the influence of the mediaeval church, it brought with it the idea of punishment. "Ecclesiastical laws and the penitentiaries looked primarily at the mental processes of the individual sinner and aimed at saving his soul. It was largely under ecclesiastical influence that the notion of wickedness became prominent and the idea was advanced that the wrongdoer should be *punished* for his wickedness in cases where wickedness could be established." (Radzinowicz and Turner, 1944.) The test of moral blame which came to be applied was, of course, one which made use of an absolute moral standard as understood by the judges and not the wrongdoer's attitude—and we have not moved far beyond this stage today.

Legal authorities, some quoted by Henderson and Gillespie (1950), generally regard the mentally diseased and defective as impaired in a power of "controlling" their conduct, which all normal people are supposed to possess. This way of thinking about the matter is common among psychiatrists also. East (1949) avers that "the faculty of self-control is impaired in most cases of insanity"; and of the normal, subnormal, mentally defective, psychopathic, psychoneurotic and psychotic that: "It will be agreed that at one end is the fully responsible offender, and at the other the psychotic who may be so insane that he is legally irresponsible. The remaining groups occupy midway positions and present different degrees of culpability as well as of social adaptability." He attempts to distinguish between "criminal responsibility", which he alleges to be a legal concept both understood and approved by the public, and "culpability", recognized by medical men. His view that "the thoughts and behaviour of the insane are to some extent related to the mental diseases from which they suffer" contrasts with the more positive and universal statement of Henderson and Gillespie that: "Medicine has come to recognize that the mind is a whole, one and indivisible. There is no mental disorder, however partial in appearance, that does not have its reverberations throughout the rest of the affected mind." MacNiven (1944) emphasizes that "there is no sharp dividing line between normal and abnormal mental functioning", that the difference is "quantitative, not qualitative", the same mechanisms being operative, albeit in exaggerated or distorted fashion; the mind functions as a whole and therefore when a mentally ill person commits a criminal act it is wrong to suppose that his conduct was uninfluenced by his illness. He comes to the conclusion that "the only logical solution to the problem of criminal responsibility is to abolish the legal concept of responsibility and to regard everyone, whether sane or insane, who commits an offence as responsible but not necessarily punishable. Strauss (1954) states: "It is clearly impossible to establish moral responsibility in the case of an insane person, for an insane person is held in law to be irresponsible."

Karpman (1949) expresses the viewpoint that criminality is a disease and criminals can be cured, and he tries to demonstrate "that *since* these people are emotionally abnormal, they cannot be held legally responsible; and that psychiatric treatment, and not punishment, is the preferred and logical treatment of crime" (italics present writer's). He cites a number of cases in support of this thesis, which can only be accepted as evidence that the persons concerned were emotionally abnormal and not as evidence that they could not be held responsible: this hinges upon acceptance of the above-mentioned premiss. "Criminal behaviour", he says, "is an *unconsciously* conditioned psychic reaction over which they have no conscious control" and "there can be no question of responsibility where there is no evidence of conscious guilt" (italics present writer's). Tappan (1952), a sociologist, however, declares that: "The criminologist is generally hesitant today to establish a strictly clinical orientation in the treatment of most offenders. He is skeptical particularly concerning the application of medical psychology to the great mass of what appear to be psychologically normal criminals or to 'emotionally deviated', 'psychopathic' or neurotic offenders where their conditions are not amenable to reasonably effective treatment modalities nor even to uniform diagnosis among the experts." (One might comment, *en passant*, that if the latter criteria were to be taken seriously medical psychology would not be applied to anyone.) Buckman (1952) puts it: "The abnormal behaviour of the delinquent has its origin in the deeper and *unaware* part of the mental life of the delinquent and he is, *therefore*, less able to manage his acts than the person who has normal emotions. The psychiatrist thinks of criminals as sick in the sense that he knows it is difficult for them to *control themselves* without therapy of some kind, and therefore he does not condemn them." (Italics present writer's.) Frank (1952), a police commissioner, has a contribution more pertinent than most; he gives two meanings of "responsibility": "In one sense, it relates to a power that one has over his own fate. There is the assumption of a free will which most criminologists deny. That concept of responsibility has been criticized as mere inference or rationalization. From a strictly scientific point of view, praise or fault cannot be attributed to any individual act. When one's conduct is examined it must be, at least, in terms of heredity and life experience." Some concept of responsibility is necessary for society to function, however, and "a person must be held accountable for his personal behaviour"—to refute the concept of free will does not relieve an offender of responsibility in this sense of accountability; this viewpoint "has found expression in the gradual acceptance by our community of a theory of protection in lieu of punishment that is merely vindictive in character".

In Scots Law, in the case of murder the concept of "partial responsibility" is permitted. Henderson (1944) quotes Lord Alness, referring to those who do not merit the description of "insane" but "are nevertheless in such a condition as to reduce the quality of their act from murder to culpable homicide"; there must be some weakness, aberration, unsoundness, "a state of mind bordering on, though not amounting to, insanity; there must be a mind so affected that responsibility is diminished from full responsibility to partial responsibility". That is to say, for responsibility to be diminished there must be some disorder or deficiency which diminishes responsibility . . . He also quotes Prichard who, as long ago as 1835, postulated " 'a form of mental derangement', something which is uncontrollable, which indicates a diseased mind, and, therefore, is not subject to reason and free will". Other factors which are allowed as reducing responsibility are tender age and alcohol, under the influence of which "a person is not fully responsible for his actions", his inhibitions against anti-social acts being undermined or paralysed (Scott, 1944). Others take a simpler, not to say more naïve, view. Rockwell (1953), for instance, says: "There are no degrees of liberty. A person is either confined or he is at liberty. The price of liberty is responsibility. If liberty is indivisible, so then is responsibility, and the concept of degrees of criminal responsibility is fallacious." In this view, only the certifiably insane criminal is relieved of responsibility.

It has been argued that the law should also make allowance for the "irresistible impulse", which is the doctrine of partial responsibility in another guise. This, naturally, has given rise to some heart-searching on the part of those who might be called upon to gauge the degree of resistibility of an impulse. "Whether a person can, or cannot, resist a desire can only be determined by studying carefully and minutely his past behaviour and past life", states Rudolf (1944). He adds: "This may take an hour or more, particularly if evidence confirming some of his statements must be obtained."(!) This assessment of controllable reaction can be computed accurately only by a trained and experienced person, of course. Lord Jowitt (1954) cites Neustatter who says: "As long as there is no proof which impulse is genuinely irresistible it would clearly be unsafe to allow it as a plea, as those who would have controlled themselves for fear of the consequences might be tempted not to do so, with consequent danger to the public."

The M'Naghten Rules, as Strauss (1954) has pointed out, were formulated at a time when man was regarded as a kind of reasoning machine: "Today we know, however," he says, "that many forms of insanity—in fact, most kinds—do not primarily impair the intellect so much as disorganize the life of the emotions, and in such a way as to deprive a man of his capacity for moral choice, or anyhow seriously to distort his perceptions of right and wrong." The British Medical Association has sought to have the much-quoted specifications (". . . the accused was labouring under such a defect of reason, from disease of the mind, as not to know the nature and quality of the act he was doing; or, if he did know it, that he did not know he was doing what was wrong") enlarged by the addition of "a disorder of emotion such that, while appreciating the nature and quality of the act, and that it was wrong, he did not possess sufficient *power to prevent himself* from committing it" (italics present writer's) and ". . . to such an extent as not to be fully accountable for his actions, they shall return a verdict of 'Guilty, with diminished responsibility.' " Wingersky (1954) writes: "Since there is blurring between the extremes of sanity and insanity, it is difficult, if not impossible, to draw a clear line of demarcation between responsibility and irresponsibility. Coupled with this ineluctable condition and the fact that a wide variety of mental abnormalities generate diminution of responsibility, [subject of the sentence missing] led the [Royal] Commissioners to their final conclusion on the proposal to introduce this doctrine into English Law", that it was "beyond the scope of this Commission's power". These quotations further illustrate the traditional presuppositions which stultify thinking about such problems as we are concerned with here.

The M'Naghten Rules embody the tendency to look not *at* but *past* the behaviour of the individual in search of some ill-defined, nebulous mental kink. Mayer-Gross *et al.* (1954) have pointed out how a quite anomalous procedure led to the crystallization, over a century ago, of a contemporary opinion, one which is now subject to much variation in its interpretation by judges, and how "the debate centres around, [*sic*] not the medical facts, but metaphysical issues of which, if they have a meaning at all, the medical man has no direct knowledge". Confusion they attribute to the use of the word, "responsible": "Lawyers seek to establish non-responsibility on the basis of evidence, when all that can be established medically is the extent of the mental abnormality of the accused, and the *decision on non-responsibility* is an *ethical judgment* to be made by judge or jury." Attention is focussed on whether the mental abnormality passes the M'Naghten test (". . . such a definition of madness, that nobody is hardly ever really mad enough to be within it", said Lord Bramwell in 1874, "yet it is a logical and good definition"), and therefore the really important clinical aspects of the case are passed over. In Slater's (1954) estimation, it "prevents the proper presentation of psychiatric evidence;

it impedes scientific advance in the understanding of the relation between mental abnormality and crime; and it throws a barrier in the way of education of the public and of officers of the law in what our scientific knowledge and understanding already are". In lesser crimes, say Mayer-Gross *et al.*, the psychiatric aspects do not receive adequate consideration in the courts; and sometimes not even in capital cases. The existence of capital punishment results in conflicts between the legal and the medical viewpoints in an acute form and with maximum publicity. No other European country is burdened with a formulation of the M'Naghten type. Moreover, under the present system, it is impossible to obtain psychiatric evidence on an impartial footing: such evidence should be called by the court and be subject to cross-examination by both sides.

## Basic Assumptions

The basic *assumptions* underlying most of the viewpoints indicated above will reward careful scrutiny. First and foremost, it is assumed that human beings possess a power or faculty of "self control" (which is indistinguishable from "free will"). Second, it is assumed that this power, present in all psychologically normal people, is impaired to a greater or lesser extent in all psychologically abnormal people—whether their abnormality is described as an intellectual or an emotional disorder or deficiency. (There has been a move away from the "all-or-none" idea of responsibility, its presence and absence corresponding to legal sanity and insanity respectively, to a graduated responsibility.) Third, it is assumed that "self-control" stands in a linear relationship to "responsibility" —if it is not actually the same thing—so that decrease in one entails decrease in the other. (From these assumptions it follows that every psychological abnormality involves some diminution of responsibility.) Fourth, it is assumed that conscious factors determine a person's conduct when he is in a normal psychological state, unconscious factors when he is in an abnormal.

No evidence or argument, psychological or logical, is adduced for either the *modus operandi* of this "faculty" or for its alleged presence in the normal and absence in the abnormal. It is not explained what is controlling what, or how. To talk of the "self" controlling the "self" is a meaningless use of words, and one which leads to an infinite regress, since the question then arises, "What controls the self which controls the self?" The "self" of "self-control" dissolves, in Smith's (1954) words, into "a series of *disconnected* interventions, irruptions into the 'causal chain.' "

## Practical Consequences

Some of the practical consequences of this way of thinking, which has normal and abnormal persons, criminal and non-criminal, all performing to the tunes of different sets of laws, are seen in the courts when psychiatrists of different persuasion appear for the defence and for the prosecution to argue the sanity of the accused. Wertham (1949) refers to the endeavours of four psychiatrists to demonstrate to be sane a man who had indulged in such practices as inserting pieces of cotton, saturated with alcohol, into his own rectum and setting fire to them; he had had a hundred child victims for similar purposes; X-rays showed twenty-nine needles in his body, which he had been sticking in between rectum and scrotum for years; he ate human flesh (said one of the psychiatrists, "There is no accounting for taste") and faeces (quoth another, "I know of individuals prominent in society—one individual in particular that we all know. He ate human faeces as a side dish with salad."). Wertham himself, however, appears to regard as psychologically normal a man who knifed his brother's baby and another, with a history of crime stretching over many years, who committed murder quite unnecessarily. For Wertham, apparently, psychopaths and simulators are normal. Other psychiatrists feel that there must be something odd about individuals who perpetrate such deeds; one senses a bewilderment, for example, in East's (1949) remarks on the case of a man who killed a woman and then ravished the corpse, finding it "difficult to believe that anyone could commit this act unless gross mental abnormality was present". As Mayer-Gross *et al.* (1954) point out: "The very horror which the abnormal features of a crime have aroused in the public and in the minds of those present in court, may prevent their appreciation as evidence of the abnormality of mind of the accused."

Another anomaly produced by this attitude we are discussing is the concern of psychiatrists over what might be their "most useful contribution to the problem of punishment", as East (1949) puts it. "Punishment", he says, "may be more effective if accompanied by psychiatric treatment", in the case of neurotics and psychopaths. He chides the armchair critic who opposes the *retributive element* of punishment and who "sometimes seems to forget that it has a deep-seated biological significance . . . In a cultured society it may be necessary, and advantageous, if it preserves a correct relation between the turpitude of the offence and the severity of the award. At the same time justice must be dispassionate, and stress the need to restrict our abhorrence and disgust to proper proportions as well as oppose pusillanimous sentimentality by vigorous understanding. Moreover, we must not confuse retributive justice with vindictive punishment; revenge may be an evil to the avenger as well as to the object of his vengeance." Unfortunately, this flourish of fine-sounding phrases does not include instruction on how to assess the "correctness" of the relation between crime and punishment or the "propriety" of the proportions of our emotions. The only difference discernible between "retribution" and "vengeance" is that the former is applied in cases where the writer approves and the latter where he disapproves of the action taken. Another essay in the same collection quotes the Hippocratic Oath: "The regimen I adopt shall be for the benefit of the patients according to my ability and judgment, and not for their hurt or any wrong." We find effort being misdirected, then, into seeking methods of simultaneously causing and alleviating suffering, for the medical practitioner can support punishment, which means causing suffering, only with detriment to his professed ethic, which means alleviating suffering.

East (1949) also writes: "The State acts, and must act, upon the assumption that men and women are mentally normal until the contrary is proved." But normality is not to be assumed, analogous to innocence: if the accused is proved guilty, i.e. physically responsible for the offence, then it follows that his behaviour has been deviant or abnormal, and to talk of "psychologically normal criminals" is a contradiction in terms, equivalent to saying, "persons who behave normally who behave abnormally".

## VIEWPOINT

In tracing the history of the development of the idea of the soul in Western philosophy and science, Ellis (1940) observes that with the practical success of the Cartesian mechanism there was a general acceptance of the associated metaphysic: vitalism arose as a compromise between Cartesianism and common-sense thought—the *psyche*, a vitalistic and anti-mechanistic principle, conferred freedom upon the human; philosophical thought, on the other hand, accepted the mechanism but repudiated the dualism, generally; the scientist, without worrying about the philosophical implications, has tested out mechanism through acceptance of it as a working hypothesis. Biological mechanism, or "behaviourism", he remarks, as a speculative idea is as old as Anaxagoras, as a mature philosophical concept as old as Descartes, as an experimental method comparatively new. "To find a mechanistic", he says, ". . . a natural explanation of biological process, may call for years of difficult laboratory work which may yield little of significance in the end. But anyone of moderate intelligence may sit in his study and evolve half a dozen highly plausible supernatural explanations in the course of an afternoon." In the words of Craik (1943), "The mechanist does not seek the things in between without reason and gratuitously. He seeks something between two events A and B just because A does not always produce B; and there is no other course open to him." Nor does a mechanistic approach take any of the complexity or richness, enjoyment or meaningfulness out of life, as some people, who use "mechanistic" as an emotive rather than a descriptive term, seem to think: how does one answer a *non sequitur* other than by pointing it out? Behaviourism, since Watson's declaration, has become the basis of all modern psychology, at least methodologically.

Modern psychology is deterministic, monistic, behaviouristic (cf. Cole, 1953). The study of behaviour is based on the premiss that every action is a product of the interplay of hereditary and environmental factors, which are but convenient ways of ordering past history and present experience. If we know the biosocial matrix of any personality, then we know the factors which have determined his conduct, be it criminal or other as defined by social mores. Any phenomenon can be traced to its origins in preceding events, theoretically: the intrusion of such an arbitrary agent as "*free will*"—*which does not mean anything if you stop to think about it*, in any case—would make a chaotic world in which scientific analysis would be impossible. "Free", like "chance", is a word to cloak ignorance. The psychology of personality bristles with difficulties because we are never in a position where we can know everything about an individual's life history. The complexity of the material under study and the early stage of development of psychology frequently make our attempts to identify the springs of specific acts quite vain.

As Boring (1933) wrote many years ago, it has been found necessary to rid ourselves of "the mystery of an 'unanschauliche Bewusstheit', the impalpable and imponderable consciousness that will not lock horns with physical reality or honestly assume a part in a closed causal system". Cole (1939), outlining the beginnings of psychology, states: "From first to last the science has been haunted by the ghost-soul of primitive animism." In a more recent essay from the philosopher's side, Ryle (1949) has effectively disposed of "the ghost in the machine". Modern philosophy has shown, in fact, that many of the problems which exercised philosophers of yore are non-existent problems, problems which arise out of wrongly posed and therefore meaningless questions, problems which are a function of the nature of language and not of the phenomena ostensibly being dealt with (some backwoodsmen of philosophy are still kicking against the pricks—particularly those with a vested religious interest). Into this category fall, among others, questions of the "body–mind" relationship and of "free will". We are not with "free will", we are not without "free will": it is just not a useful or meaningful way of talking about life. In Stevens's (1951) words: "The traditional but somewhat antiquated problem of psychophysical dualism is exclusively a problem of syntax. Using the common 'material mode' of speech we might say: To every psychical state there is a corresponding physical state of the body and the two are lawfully connected. Couched in this form, such a sentence is a veritable gold mine for pseudo-problems."

Now the notion of "responsibility", as it is commonly used, is rooted in these ideas, of "mind" and "free will": it is "the ghost in the machine" that is held responsible for the individual's conduct, or misconduct. If it was a sick ghost at the time of the misconduct, say the forensic pundits in effect, then it may be excused punishment; a very young or a very drunk ghost may also be treated magnanimously; otherwise it is culpable (animals other than human never being responsible). It is suggested further that the ghost may be allowed to have irresistible "impulses", which would absolve it from its sins.

The question of irresistible impulse is, of course, a purely hypothetical and metaphysical one: all impulses which have emerged into action have *ipso facto* been shown to be "irresistible" impulses. Who are you or I to say that the arraigned "could have" resisted the impulse "if he had tried to", or that he "could have" made the effort "if he had wanted to", anyway? The impulses and actions are determined by influences not under the control of any ghost-soul. (By "irresistible" in these discussions "sudden, irresistible" impulse is usually meant—but that is neither here nor there.) With reference to Neustatter's remarks (q.v.), apart from the fact that there never could be proof that an impulse was irresistible—and it might be recalled here that no two situations are ever the same, either for different persons or for the same person—it is true that knowledge of the existence of such a law by an individual would be a part of the complexity of previous experience forming the matrix of his present conduct—but not necessarily a significant or a "conscious" part, nor one operating in the way imagined by those who regard the criminal as a creature motivated by pure reason, as they themselves understand it. It might also be noted that implicit in such statements about "danger to the public" is the unwarranted assumption that recognition of psychiatric factors means that the criminal "gets off" and that no appropriate remedial measures are to be taken. The proponents of the "irresistible impulse" are presumably believers in free will, since all impulses which have been acted upon must be "irresistible" for the determinist—if this formulation means anything to him. The free will, then, is subject to limitation by uncontrollable impulses, forces which it cannot resist. But how can the irresistible force move the immovable object? Or are there certain regions where free will operates and others where it does not—if so, what are these and how are they defined? Such questions visibly enough spring from a play upon words. The fundamental criticism is that our universe is not populated by a species of impulse omnipotent over human beings, periodically galvanizing individuals into action: such things as "impulses" are never discovered, they are invented, parts of a system which we impose upon the world of our immediate experience for particular purposes, constructed as part of a model to explain and predict behaviour. As Boring (1933) put it: "One does not attempt to discover conscious elements, attributes, or dimensions; one makes them up and uses them as phenomenological exigencies require."

The basic objection, Smith (1954) states, is not so much to the libertarian's refusal to accept mechanical or para-mechanical determinism as an account of moral choice as to the ease with which he accepts it as an account of non-moral choice. The division of labour between the free-floating ghost and the lawful determining factors of these cosmologies is not made clear. It is evident, however, that for those who think in the conventional, lawless, ghost-in-the-machine framework it is only when there is some striking factor in the previous history of the individual, obvious to laymen—as in some cases of gross mental disease or deficiency, drunkenness or infanticide—that responsibility is to be regarded as diminished, are psychologically operative factors to be recognized; in other cases, it is the ghost. Thus the allocation of responsibility is tied to the jury's microscopic understanding of psychology. Healthy ghosts are free, sick ones are determined—this is the crux of the matter. This curious view, that only in disease and not in health do psychological factors work, is reflected in several dichotomies: conscious–unconscious, responsible–irresponsible, free–determined, inhibited–uninhibited. The relation between abnormality and responsibility is explained no more than is the functioning of the free, conscious, responsible and elusive ghost, be it in the pineal gland as Descartes suggested, in the navel as D. H. Lawrence had it, or elsewhere.

What, then, is this feeling of "free choice" which some people complain about? And how does it come about that we can and do talk of "alternative" possible modes of action? These phenomena can be seen as results of a confusion of logical categories and of a misunderstanding of the epistemological status of words and concepts. "All science necessarily presents, it seems to us, but a map and picture of reality. If it were to present reality in its whole concreteness, science would be not a map but a complete replica of reality and then it would lose its usefulness" (Tolman, 1932). The different sciences are like maps of the same country ("reality"), charted by the same method (the "scientific"), differing only in scale (Woodworth, 1948); each develops its own interwoven system of special techniques and terminology, however, and confusion frequently arises when there is an inadvertent slip from one scale with its appropriate set of concepts into a neighbouring one, and perhaps back again (e.g. between psychology and physiology). Another source of confusion is the sidling from one logical category, in the use of words, into another—as described by Ryle (1949) and others. Perhaps more common is the shifting between one particular mode of scientific thought and everyday, "common-sense" experience—developing a serial system as an observer of events (especially when these events are language behaviour) and then inserting "subjective" concepts into it at different points. This is a confusion of map with reality. The feeling of "free choice" merely describes at the level of immediate awareness or common parlance the condition where, in more psychological terms, an organism pauses at a "choice" point. Alternative "possibilities" are, in fact, not "possible" at all: only one thing happens, only one thing *can* happen—and that is the only possible one. The existence in our language of terms and constructions of this sort is a result of the fact that frequently we are unable to predict with certainty, for lack of knowledge, and must talk about "possibilities" which do not exist in fact, in the "external world of reality", but which are hypotheses that we have formulated, existing within our symbolic systems, to which we may attach varying degrees of probability, being ignorant of which one coheres with reality. As Craik (1943) expressed it, our self-consistent combinations of patterns of nervous excitation (i.e. our "alternative possibilities") may not have counterparts in external physico-chemical combinations: "In causal chains and physical or chemical combinations, the possibility of a given combination tends to be limited by other factors than the mere self-consistency of the combination", the nervous system only has "to produce combinations of excited arcs, not physical objects; its ‘answer’ need only be a combination of consistent patterns of excitation—not a new object that is physically and chemically stable.”

What now becomes of morality? A consequence of the “naturalist’s” (i.e. determinist’s) attitude, says Wienpahl (1953), is that justifiable punishment be of an educative nature, and it entails that “there is no difference between the criminal and the non-criminal”—“our treatment of all individuals who violate laws will differ in complexity, for example, but not in kind”. If the fact is accepted, that the concept of free will is meaningless, does it then follow that there is no such thing as a morally guilty person? This objection, that it means that there is no morality, is shown by Wienpahl to rest upon a form of the “incompleteness argument”—the inference is a valid but a misleading one. “. . . The implication of relinquishing the concept of free will is not that there is no morality. The implication is rather that the words ‘moral’ and ‘morality’ have no special, unique and unalterable meaning.” As in the case of all other words, the meaning depends on the context. The objection, then, is based on another of these ubiquitous confusions in language usage, the kind of thing which it is the job of the philosopher to resolve. The conclusion is not that *there is no morality*—this is a “*pseudo-object statement*”—but that a time has come when circumstances indicate that a new usage is required: at such a time we are confronted with a question which is neither factual nor logical but “philosophical”. “As long as we believed in gods or a God in an experimental way”, says Wienpahl, “and as long as psychological information was thoroughly inadequate, the old concept of moral responsibility worked. Circumstances have gradually indicated a new usage for ‘moral responsibility’ and the naturalists have, for all practical purposes, clarified this usage. Some of the motivation behind the incompleteness argument, therefore, may stem from the familiar reluctance to give up an old usage of a term, a reluctance which is understandable since any term is related to a family of terms. The family of ‘moral responsibility’ included ‘sin’, ‘guilt-with-the-additional-meaning’, ‘free will’, ‘God’s word’, ‘hellfire’ and ‘damnation.’” In deciding whether an individual is to be held morally responsible, he says, all that we need to know is whether his behaviour was performed without constraint by others and whether there is a reasonable expectancy that we can influence his future behaviour by rewarding or punishing him for what he has done.

## CONCLUSION

The concepts of responsibility and punishment popular in legal and psychiatric practice are theological and metaphysical anachronisms, hangers-on of the “mind” and “free will” which are so firmly entrenched in both lay and medical mind—and so incorporated in our language that it is often impossible to avoid using them. The diagnosis of sanity is, if anything, less arbitrary than the diagnosis of responsibility and not more so, as Lord Jowitt (1954) appears to think. A jury is a quite inappropriate body to make any such diagnosis; this is difficult enough, in all conscience, for the psychiatric specialist. The task of the jury is, or should be, to ascertain the facts in the sense of what actually happened when the alleged offence took place and not in the sense of whether the accused person is psychologically abnormal.

“Cool, unexcited bystanders often demand that a criminal trial should be conducted as quietly as a scientific enquiry . . . The truth is that litigation of all sorts, and especially litigation which assumes the form of a criminal trial, is a substitute for private war, and is, and must be, conducted in a spirit of hostility which is often fervent and even passionate." These are the words of Sir J. Fitz-James Stephen, quoted by Henderson and Gillespie (1950). That diagnosis can become, and frequently is, both inside and outside the courts, a topic for subjective argument rather than a matter of objective allocation follows from the uncertainty of so embryonic a branch of medicine. Adoption of such a system as that of Sweden, described by Mayer-Gross *et al.* (1954), would obviate the unprofessional practice of certain medical men who act as expert witnesses for defence and prosecution, which can hardly be avoided in the present system. In Sweden, psychiatric evidence is given exclusively by specialists in the service of the State and is concerned not only with the accused's psychological condition at the time of the act but also with the most appropriate remedial measures. Where psychiatric treatment is indicated, the administrative method of dealing with the case is no different from that in other cases where the patient is a social danger but has not committed a crime, and admission to an ordinary psychiatric hospital is the mode of disposal. Here is the answer to those who might object that it is impracticable to do away with present ideas of responsibility. There has been, in fact, a total abandonment of the concept of medico-legal responsibility. "The pragmatic solution of the question, 'What are we to do with this man?' is regarded as the important task, rather than the theoretical solution of the question, 'How are we to adjudge this crime?' " (Slater, 1954).

Relegating questions of responsibility, and with them those of punishment, to the amusement of the religious and others of that kidney, we are left with the important and practical question of the disposal of the convicted. East (1949) quotes the Gluecks who, in 1930, stated that "legislative prescription of penalties, and judicial sentencing are founded upon considerations almost wholly irrelevant to whether or not a criminal will thereunder ultimately be a success, a partial failure, or a total failure". The law does not change much in a quarter of a century. There is, moreover, both clinical and experimental evidence (cf. Maier, 1949) to support the view that punishment has an opposite effect to that desired, at least in certain circumstances. We are concerned not with the past but with the future of the individual and of the community: what is the best course of action, in the light of all available knowledge, in order to promote the harmonious adjustment of this individual within the community? (In particular cases, the action might be the same as was formerly regarded as "punishment", but that would be fortuitous.) The answer is to be sought in the same manner as the answer to any problem in science, looking at one's material, be it sub-atomic particles acting in certain fields of force or human beings acting in their milieu, so far as possible in an impersonal, objective and detached fashion. Then, with purpose clearly stated and method delineated, appropriate action may be decided upon. Questions of "mad" or "bad", with their value-judgments and emotional loadings, do not arise. We are confronted with a person who has committed some action that is abnormal, by its infrequency of occurrence, and that has brought its doer into conflict with his fellows; we have to decide how to obviate or minimize repetition of such conflict, for the good of all concerned. In the present state of scientific knowledge and social organization, it will be a long time before satisfactory answers can be arrived at.

## SUMMARY

It has been pointed out that the question of responsibility is not a medico-legal but a philosophical-psychological one.

Current legal and psychiatric notions about responsibility have been described, the assumptions on which they are based made explicit and their practical consequences indicated.

It has been shown that the ideas of responsibility and of punishment, derived from a background of outmoded "body-mind" dualism and theological "free will", subserve no useful purpose and that, on the contrary, they obscure clarity of thought and obfuscate issues of practical human importance. The feeling of "free choice" and the awareness of "alternative" paths of action have been interpreted as properties peculiar to the human symbolic system and not to the external universe.

In a world of science, based on determinism, the old ideas of "responsibility" and "punishment" should be discarded. This does not mean that henceforth there is no "morality", but that such terms take on new meaning in a new context. Pursuance of the scientific approach to the trial and disposal of criminals is advocated.

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*Insulin Coma Therapy in Schizophrenia*

1. Insulin coma therapy at the Pennsylvania Hospital produced an immediate improvement or remission in 67·7 per cent. of 780 patients treated between 1936 and 1951.

2. At least 334 patients, or 63·3 per cent. of all patients who originally improved, had a relapse; 44 per cent. of all these relapses occurred within 30 days, and 78 per cent. within 1 year of treatment. A second insulin course brought about an improvement or remission in 52 per cent. of 122 patients who had relapsed.

3. Factors associated with the most favorable prognosis include: age over 16, psychosis of less than 6 months' duration, with a clinical picture of paranoid, catatonic, or undifferentiated schizophrenia; and if during treatment the patient receives at least 30 to 60 coma hours and gains more than 30 pounds in weight.

4. The authors conclude that insulin coma therapy is effective in restoring the schizophrenic patient to his prepsychotic adjustment. This restoration to health is not accompanied by a permanent correction of the factors that predispose the patient to regress to schizophrenia.

(Authors' Abstr.)

*The EEG Changes in Unilateral and Bilateral Frontal Lobotomy*

1. In cases of unilateral and bilateral frontal lobotomy, temporal slow wave activity was found to be a prominent feature, though more transient than the dominant frontal slowing. This non-frontal slowing may be interpreted as the result of cerebral edema and hippocampal herniation from operative manipulation.

2. There is an apparent correlation between the degree of slow activity in the post-operative EEG and clinical improvement, in that slight or severe degrees of slowing were found to be more conspicuous in those cases that exhibited little clinical improvement. In contrast, moderate slowing was associated with moderate to marked clinical improvement.

3. The frontal slow wave activity, though decreasing in prominence, persists in the majority of cases for at least 3 years and possibly longer.

(Authors' Abstr.)

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* A number of abstracts in this section are reproduced from *Chemical Abstracts*. To the Editors of this Journal we extend our grateful thanks.

### *The Effect of Adrenochrome and Niacin on the Electroencephalogram of Epileptics*

1. Adrenochrome in dosages of 10 mgm. does not change the EEG of normal volunteers, but in 10, 25 and 50 mgm. doses increases the bilateral paroxysmal abnormalities in the EEG of epileptics, but has very little effect on the cortical focus itself.

2. Nicotinic acid given orally or intravenously in normal volunteers showed a slight shift in EEG frequency to the fast side; in epileptics the drug considerably decreases the bilateral diffuse paroxysmal abnormalities (except in true idiopathic epilepsy), but has very little influence on the focus itself.

3. The mode of action of the above-named drugs is discussed.

4. A tentative explanation is offered as to the genesis of the paroxysmal EEG disturbance in schizophrenia.

(Authors' Abstr.)

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### "*Protein Profile*" *in Multiple Sclerosis*

Electrophoretic serum protein fractions of 43 patients with typical multiple sclerosis were studied. Simultaneous determinations of the cerebrospinal fluid total proteins, gamma globulins, and gamma globulin-total protein (G.G./T.P.) ratios were performed in 41 of these cases. The combined results of these protein changes are termed the "protein profile" of multiple sclerosis.

Of these 43 patients, 77 per cent. showed statistically a significant decrease in their electrophoretic serum albumin and A/G ratio values, concomitant with a significantly elevated alpha-2 and/or beta globulin fraction and a normal (or slightly elevated) gamma globulin value. Significantly elevated cerebrospinal fluid gamma globulin levels and/or (G.G./T.P.) ratios were found in 93 per cent. of the 41 patients studied. Of these 41 cases, 73 per cent. gave significant changes in both biological fluids or exhibited a positive "protein profile". Statistical analysis of both serum and cerebrospinal fluid data showed no overlap of the ranges of the normal and multiple sclerosis populations except for total protein, alpha-1, and gamma globulins.

For the purpose of following the clinical course of the disease over extended periods of time by means of serum electrophoretic patterns, a new graphic method, termed the "serogram", was devised. The average mean normal values (140 subjects) for each protein fraction is represented by a straight line. Deviations from this straight line are expressed as units of standard deviation (S.D.) for each fraction in grams per 100 ml. The reproducibility of the electrophoretic serum protein data for normal subjects if readily demonstrated by means of the "serogram". It therefore permits the rapid evaluation of serum protein changes during the clinical course of a disease either in individual cases or for the group as a whole.

In accordance with the slowly progressing course of multiple sclerosis, the serograms of the group show only a slight shift toward abnormal values on repeat studies after a time interval of one and a half to two years. However, marked accentuation of the "serogram" data was found in three patients whose clinical course deteriorated rapidly.

The patient material studied consisted of two groups: (1) 32 institutionalized patients, with an average disease duration of 22 years, and (2) 11 V.A. cases, with an average disease duration of 8 years. The characteristic serum protein pattern was found in 91 per cent. of the cases in Group 1, while only four patients of Group 2 showed this change. On the other hand, 90 per cent. of the patients in Group 1 disclosed the typical cerebrospinal fluid protein changes, as compared with 100 per cent. in the V.A. group. These findings indicate that the protein changes in the spinal fluid occur prior to those in the serum.

Studies are now in progress on the application of the "protein profile" to neurological disorders other than multiple sclerosis. It is thus hoped to obtain laboratory data useful in differentiating such diseases from multiple sclerosis, as well as in elucidating some of the etiological mechanisms of these neurological conditions.

(Authors' Abstr.)

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*Changes in the EEG and in the Tendon Jerks Induced by Stimulation of the Fornix in Man*

The human fornix was stimulated under light ether anesthesia and in the vicinity of the interventricular foramen; as a result, the electrical activity of the cortex showed an increased voltage and a reduced frequency in the homolateral frontal areas. Augmentation of the stimulus intensity or of its total duration caused a more marked slowing and, at the same time, a similar though less marked response could be visualized on the convexity of the whole ipsilateral hemisphere or even over the contralateral side. In a single case studied under local anesthesia, a comparable electroencephalographic effect was observed and, simultaneously, the patient looked and felt somnolent. Bilateral cingulectomy does not abolish these results but, after prefrontal lobotomy, no slowing appears in the isolated frontal regions.

Similar stimulations caused an increase of the homo- and contralateral knee and ankle jerks.

The significance of these results is briefly discussed.

(Authors' Abstr.)

*Clinical Correlates of the Spike-wave Complex*

Out of 2,000 consecutive EEGs of neurologic patients, 121 (or 114 patients) had spike-wave complexes. Clinically, the spike-wave complex is practically diagnostic of epileptic phenomena. Spike-wave complexes are divided into the "classical" type, which correlates best but not exclusively with petit mal epilepsy; other generalized spike-wave dysrhythmias of which the multiple spike-wave corresponds most closely to grand mal epilepsy; and focal spike-wave, in which group focal seizures are more frequently found. Known etiologic factors and positive neurologic signs are rare in the "classical" spike-wave group and common in the focal spike-waves. Activation techniques are important in eliciting spike-wave complexes.

(Author's Abstr.)

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*Cerebral Metabolism of Glutamic Acid in Multiple Sclerosis*

The cerebral metabolism of 19 normal subjects and 32 patients with multiple sclerosis has been studied by the Kety-Schmidt technique with special reference to the cerebral metabolism of glutamic acid and its amide glutamine.

Measurements of cerebral metabolic rates for oxygen, $CO_2$, glucose, pyruvic acid, and lactic acid have also been made. Amidation of glutamic acid to its amide glutamine was found in 15 of 19 normal subjects. Failure of amidation occurred in 27 out of 32 with multiple sclerosis.

Intravenous administration of sodium succinate reversed the defect in the direction of amidation or utilization in half of the patients with multiple sclerosis. It is suggested that the failure of glutamic amidation in patients with multiple sclerosis may reflect a failure of one mechanism for elimination of ammonia from the brain.

(Authors' Abstr.)

*Nature and Extent of the Biochemical Lesion in Human Epileptogenic Cerebral Cortex*

The cases are presented as an apparent confirmation clinically of results obtained *in vitro* with glutamine and asparagine on epileptogenic brain tissue. The doses are admittedly large, but are diluted after administration. They must penetrate both the blood-brain barrier and the nerve-cell membrane barrier in sufficient concentration to be effective. The two compounds have no apparent effect *in vitro* or *in vivo* on normal nervous tissue function so that they are not "drugs" in the usual sense of the word. They are naturally occurring compounds which are normally consumed in the diet and normally present in body fluids and tissues of man. They are the first compounds administered to seizure patients with promising results, which are based upon an indication derived from metabolic studies on human epileptogenic brain.

(Author's Abstr.)

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*Psychosomatic Study of 46 Young Men with Coronary Artery Disease*

Psychiatric interviews, a detailed social inventory, and a battery of psychological tests were carried out upon a group of 46 young men with coronary artery disease and upon 49 healthy control subjects. All these men had already been studied carefully and data concerning medical history, anthropological measurements, and blood chemistry were available. After consolidating the information gathered by various means, the two groups were compared in terms of personality factors and also in other ways, including family incidence of cardiovascular disease, history of stress and strain, somatotype, and blood lipid levels.

The coronary patients had tended to work harder, under more stress and strain, although this was not necessarily physically strenuous work. Only a few more of the coronary patients than controls showed a consistent tendency toward compulsive striving, ascetic self-discipline, and great need to "get to the top" in their chosen work. When the two groups were compared in terms of specific personality traits, the differences were very slight. The coronary group showed less tendency to introspection than did the controls and more difficulty in handling their aggressive tendencies. The similarities between the groups were more striking, however, than were the differences, and their findings, in the main, did not confirm previous observations.

The authors found no convincing evidence that the personality differences exhibited by the coronary patients, as compared to the control subjects, could be implicated as significant factors in the genesis of coronary artery atherosclerosis. The effect of personality factors and emotional conflicts upon individuals with already diseased coronary arteries is important, but was not the primary topic of their investigation and was not discussed in detail.

The data suggested to them that the major factors in the genesis of atherosclerosis included maleness, body build, and some intrinsic metabolic fault, probably inherited.

(Authors' Abstr.)

*Glutathione Metabolism in Men under Psychological Stress* .

Blood reduced glutathione concentration is significantly diminished 5–10 hours after such psychological stresses as jumping from a 34-foot tower while in harness, parachute jumping, and participation in night-infiltration exercises, but not after extremely severe, purely physical activity. The exact nature of the psychological stress capable of evoking this metabolic response is unknown. It is postulated that severe psychological stress operating over long periods may produce irreversible depression of the blood glutathione level and its associated metabolic dysfunctions.

(Authors' Abstr.)

*Effects of Cortisone on Psychiatric Patients*

Studies on 16 subjects were made to determine whether behavioral changes occur as a result of cortisone therapy. All subjects were treated exactly alike, except that half the group were given tablets containing cortisone and half were given placebo. A battery of psychiatric and psychological tests was administered: two forms of interview; part of the Wechsler-Bellevue Adult Intelligence Scale; the Rorschach test; part of the Thematic Apperception test; the Level of Aspiration Board; and an incomplete sentence test. Tests were administered to subjects before medication, after 30 days of medication, and after a follow-up period of no medication. Selected tests were also administered between 72 and 120 hours after the onset of medication. No one in the hospital other than the physician assigning medication knew which subjects actually received cortisone. Dosage was decreased from 300 mg. on the first day and to 75 mg. on the fifth day, and remained constant thereafter until the thirtieth day.

Differences between the group receiving cortisone and the group receiving only a placebo in test behavior were minimal. Clinical judgments of five observers tended to discriminate between the groups more accurately than did the tests. Certain methodological difficulties are pointed out and suggestions made for future investigations.

Although the results are limited by the small number of subjects and the wide range of individual differences in the group, they tentatively conclude that behavioral changes following the administration of cortisone do not occur in easily detectable form nor in a manner which is uniform from individual to individual.

(Authors' Abstr.)

## 1. Biochemistry, Physiology, Pathology, etc.

*Polysaccharide Metabolism in Brain Tissue with Various Kinds of Stimuli of the Central Nervous System. Khaïkina, B. I., et al.* [*Doklady Akad. Nauk. S.S.S.R.*, **96,** 347 (1954).]

Experiments with rabbits showed that total glycogen in the brain increases after stimulation with pervitin or cardiazol; the bound fraction of glycogen rises similarly. Pervitin increases the activity (synthetic) of phosphorylase which synthesizes polysaccharides, but the hydrolytic activity is raised but slightly. Prolonged administration of pervitin, however, lowers the brain glycogen.

G. M. Kosolapoff (Chem. Abstr.)

*Manifestation of Pyruvic Acid Accumulation in the Nervous System. Dobrovolskaïa-Zavadskaïa, N.* [*Ann. Méd.* (*Paris*), **54,** 525 (1953).]

Pyruvic acid renders the vascular wall more permeable, which causes transudation into the perivascular spaces with compression of the vessels. The accumulation of pyruvic acid is frequently the consequence of a vitamin $B_1$ deficiency. Pyruvic acid plays a role in polyneuritis, parkinsonism, multiple sclerosis, cerebral arteriosclerosis, and various other nervous disturbances.

A. E. Meyer (Chem. Abstr.)

*A Second Case in the Same Family of Congenital Familial Cerebral Lipoidosis Resembling Amaurotic Family Idiocy. Brown, N. J., et al.* [*Arch. Disease Childhood*, **29,** 48 (1954).]

The formalin-preserved brain of this 7-week-old infant contained a cholesterol concentration nearly 4 times that of a similarly treated brain from a control.

Kathryn Knowlton (Chem. Abstr.)

*Substance P in the Human Brain. Zetler, Gerhard and Schlosser, Lucie.* [*Naturwissenschaften*, **41,** 46 (1954).]

Previous work on cow brain was continued. The substance P (1) content of 22 different parts of the human brain is given; individuals were from 22 to 82 years old; analysis was made 14–42 hours after death. In units per g. moist weight the (1) content varies from 1·6 in the corpus callosum to 247·6 in the ala cinerea and 698·8 in the substantia nigra. Compared with the choline acetylase content of the same areas in dog brain it seems that, particularly in the mesencephalon area, the two show opposite tendencies; high (1) content is likely to have low acetylase value.

B. J. C. van der Hoeven (Chem. Abstr.)

*Potassium Content of Cerebrospinal Fluid. Siegrist, H., and Meyer, H. H.* [*Klin. Wochschr.*, **32,** 549 (1954).]

In 138 specimens the K concentration ranged from 6·22 to 23·05 mg. per cent., with a mean of 12·84 mg. per cent. No relation could be found between K content and neurologic or psychiatric disorders. Meteorological influences on the K concentration were discussed.

Erich Heftmann (Chem. Abstr.)

*Effects of Vigorous Physical Exercise on Cerebral Circulation and Metabolism. Scheinberg P., et al.* [*Am. J. Med.*, **16,** 549 (1954).]

Exercise produced a decrease in cerebral vascular resistance (I) blood $CO_2$ (II), and pH, an increase in cerebral O consumption (III), and no significant alteration in arterial glucose. No correlation could be made between (II) and pH, and the alterations in cerebral circulatory or metabolic functions. A close correlation was found for (I) and (III).

Joseph Harris (Chem. Abstr.)

*The Permeability of Brain Slices to Citrate. Coxon, R. V.* [*Congr. intern. biochim., Résumés communs., 2e Congr., Paris*, 1952, 32–3.]

Experiments on the oxidation of pyruvate in various preparations of pigeon brain were done. In the case of slices of brain, most of the citrate formed remained within the slices and very little diffused into the surrounding medium. When citrate was added to the medium, only a little diffused into the slices. The significance of these findings is considered.

W. C. Tobie (Chem. Abstr.)

*Brain Lecithin. Klenk, E., et al.* [*Hoppe-Seylers Z. physiol. Chem.*, **292,** 241 (1953).]

Lecithin (1) obtained from human brains showed only traces of choline-containing acetal phosphatides when purified by chromatography. Oleyl-stearyl-lecithin, $C_{44}H_{86}O_{8-}$ NP.$H_2O$, $(x)^{20}_{D} +5\cdot36°$ purified by the $CdCl_2$ addition compound, refluxed 1 hour with 4 per cent. HCl–MeOH, the Me esters extracted with petroleum ether, fractionally distilled *in vacuo*, then recrystallized from $Me_2CO$ gave 30 per cent. $C_{16}$, 10 per cent. $C_{18}$, and 1·5 per cent. $C_{20}$ saturated, and 3 per cent. $C_{16}$, 46 per cent. $C_{18}$, 8·5 per cent. $C_{20}$, and 0·6–4·3 per cent. $C_{22}$ unsaturated esters calculated as the fatty acids.

David Stefanye (Chem. Abstr.)

*Antagonistic Action of Cholinolytic and Anticholinesterase Compounds on the Activity of the Higher Nervous System in Man and Animals. Mikhel'son, M. Ya., et al.* [*Byull. Eksptl. Biol. i Med.*, **37,** *No. 2*, 7–12 (1954).]

In dogs with preestablished conditioned reflexes, intramuscular injection of 1–5 mg. per kg. of pentaphen (Parpanit) abolished the conditioned reflexes. Simultaneous injection of 0·03 mg. per kg. of prophysostigmine (proserine) abolished the effects of pentaphen and the conditioned reflexes were normal. In white rats, atropine or scopolamine (1 to 5 mg. per kg.) also seriously interfered with preestablished conditioned reflexes, and prophysostigmine prevented the interference by either atropine or scopolamine. Intramuscular injection of 3 to 5 mg. per kg. of pentaphen in man induced serious psychic disturbances which were prevented by the simultaneous administration of prophysostigmine (0·02 mg. per kg.). The fact that atropine-like compounds can compete with acetylcholine in choline-accepting systems, inducing alterations in psychic activity, indicates importance of these systems in the functions of the brain. Physostigmine and prophysostigmine prevent the destruction of acetylcholine and thereby increase its effects. The importance of cholinergic systems in the function of the brain is thus indicated.

J. A. S. (Chem. Abstr.)

*Synthesis of Adenosinetriphosphate in Slices of Brain Cortex. Acs, G., et al.* [*Kisérletes Orvostudomány*, **5,** 466 (1953); *Ukrain. Biokhim. Zhur.*, **25,** 17 (1953).]

The cortex of *in vivo* frozen rat brains contains 1·0–1·5 mg. adenosinetriphosphate (I) per g. fresh tissue. Slices of brain cortex prepared from the decapitated animal contain only 0·2–0·3 mg./g. (duration of necessary operations 5–10 min.). If the slices are shaken in a mixture of 95 per cent. $O_2$ and 5 per cent. $CO_2$ in glucose (II)-containing saline, a resynthesis of (I) takes place. In rat brain cortex slices the content of (I) rises to 0·6–0·8 mg./g., in those of guinea pig to 1·0 mg./g. In presence of (II) this value is maintained for at least 40 minutes. The slices lose up to 50 per cent. of their nucleotides, adenine and ribose appearing in the supernate. The loss is more than can be accounted for by the injury of surface layers. The *in vitro* resynthesis of (I) requires O and (II). Of all substrates tested (II) is the only one which results in the resynthesis of 0·6–0·8 mg./g. (I) In presence of succinate, pyruvate, malate, glutamate, and aspartate, O consumption is raised as well as in presence of (II), yet the (I) level is only 50 per cent. of that obtained by (II). This is regarded as a biochemical proof of the fact that (II) is the only adequate substrate for brain cortex. It is concluded that instead of the rate of respiration the (I) content of slices should be used as a reliable indicator of their physiological condition. When glutamate is given to the slices with glucose, the content of (I) is less than in absence of glutamate. The effect depends on the concentration of glutamate, 0·01 M causing a 50 per cent. depression of (I) content. From determination of the rate of glutamine formation it is concluded that the latter process uses up the high-energy phosphate to such an extent that a decrease of (I) results.

F. B. Straub (Chem. Abstr.)

*The Role of the Reactive Groups of Proteins in the Functioning of the Nervous System. Kochtoyanz, Ch.* [*Congr. intern. biochim., Résumés communs, 2e Congr., Paris*, 1952, 436–7.]

If the SH groups of the proteins of the pneumogastric nerve are blocked, the action of the heart and of the skeletal (voluntary) muscles is impeded. The action of acetylcholine on the heart is also inhibited. Liberation of the SH groups restores the former activity. In voluntary muscle fatigued by prolonged stimulation of the nerve, cysteine causes the abolition of fatigue and restores nerve function. Urea has the same action by freeing SH groups of the proteins. If an isolated cervical superior sympathetic ganglion is perfused with a $CdCl_2$ solution, stimulation of the preganglionic nerve no longer produces contraction of the nictitating membrane, probably since the Cd blocks the SH groups. Subsequent perfusion with a cysteine solution restores nerve activity by permitting the liberation of the acetylcholine. Blocking the SH groups of the innervation of the small intestine reduces the secretion of digestive enzymes.

W. C. Tobie (Chem. Abstr.)

*Note on the Free Amino-acid Content of Rat Brain. Ansell, G. B., and Richter, D.* [*Biochem. J.*, **57**, 70 (1954).]

In addition to the usual amino-acid pool of tissues, the brain tissue contains a small group of compounds (glutamine, glutamic acid, and γ-aminobutyric acid) in relatively high concentration with a special function. The glutamic acid apparently occupies a central position in the metabolism of the brain and has the unique ability to undergo oxidation, amidation, transamination, and decarboxylation. The decrease by about 2·6 mg. per cent. in the free amino N of the rat brain in pentothal anesthesia is ascribed chiefly to a fall in the glutamic acid level. Nine amino compounds appear in paper chromatograms of deproteinized extracts of rat brain.

S. Morgulis (Chem. Abstr.)

*Substance P in the Central Nervous System of the Cow. Zetler, G., and Schlosser, Lucie.* [*Naturwissenschaften*, **40**, 559 (1953).]

Results are reported on analysis of 11 regions of the cow brain for substance P (the method of Pernow is used). The ala cinerea has the highest concentration 486·4 Pernow units per g.

B. J. C. van der Hoeven (Chem. Abstr.)

*Central Nervous Function and Changes in Brain Metabolite Concentration. III. Glycogen in the Normal Behavior of Mice. Chance, M. R. A.* [*J. Exptl. Biol.*, **30**, 468–74 (1953).]

Increases in glycogen content of the brain occur after a jump, a fall, or after aggressive behavior in a fight. No increase was found during sleep, after running or walking, or after defensive behavior in a fight.

Lawrence P. Miller (Chem. Abstr.)

*Ammonia and Glutamine in the Brain at Increased Oxygen Pressure. Gershenovich, Z. S., and Krichevskaya, A. A.* [*Doklady Akad. Nauk. S.S.S.R.*, **95**, 837 (1954).]

White rats were subjected to pressure-chamber experiments under 4 and 6 atmospheres of pure O, the experiments being run until the end of convulsion periods, after which the animals were decapitated and the brains immediately frozen in liquid air and analyzed for $NH_3$, glutamic acid, and glutamine. Increased O pressure increases the $NH_3$ content of the brain (shown graphically), even in the preconvulsion stage, while the convulsive stage does not necessarily signify a still higher $NH_3$ content. Almost complete disappearance of glutamine from brain tissue is noted previous to the convulsions. The amount of free glutamic acid, on the other hand, rises, especially in the convulsive stage.

G. M. Kosolapoff (Chem. Abstr.)

*Function of Glutamic Acid in Nerve Tissue. Weil-Malherbe, H.* [*Naturwissenschaften*, **40**, 545 (1953).]

A lecture dealing with the $NH_3$ content of nerves, enzymic reactions of glutamic acid in nerve tissue, glutamic acid as energy source, its effect in hypoglycemic coma, and psychological effects.

B. J. C. van der Hoeven (Chem. Abstr.)

*Oxygen Consumption of the Brain at Various Ages of the Albino Rat. Weill, J. D., and Mandel, P.* [*Compt. rend. soc. biol.*, **147**, 1818 (1953).]

The O consumption is low for the first 14 days after birth, then rapidly increases nearly to the adult level in the next few days.

L. E. GILSON (Chem. Abstr.)

*Cerebrospinal Fluid of Normal and Vitamin A-deficient Swine as Determined by Lumbar-puncture Method. Sorensen, D. K., et al.* [*Am. J. Vet. Research*, **15**, 258–60 (1954).]

An increase in cerebrospinal-fluid pressure up to 220 mm. was observed in pigs which were deficient in vitamin A, against 80–145 (av. 109·5) mm. in normal pigs. The lumbar-puncture method can be used to detect the onset of vitamin A deficiency.

RUDOLPH SEIDEN (Chem. Abstr.)

*The Histochemistry of Cholinesterase Activity in the Nervous System. Csillik, B., and Sásay, Gy.* [*Acta Morphol. Acad. Sci. Hung.*, **4**, 103 (1954).]

In using a modified Nachlas-Seligman naphthyl acetate technique, stable cholinesterase (I) was localized in the cytoplasm of autonomic and sensory ganglion cells, in postganglionic fibers, in motor end plates, and in tactile corpuscles. Labile (I) was localized in the larger sensory ganglion cells, peripheral myelin sheaths, and in the intercellular substance of the gray matter. Glial, Schwann, and connective tissue cells gave negative reactions.

JOHN F. LHOTKA (Chem. Abstr.)

*Brain Acetylcholinesterase Activities in Rabbits Exhibiting Three Behavioral Patterns Following the Intracarotid Injection of Diisopropyl Fluorophosphate. Aprison, M. H. et al.* [*Am. J. Physiol.*, **177**, 175 (1954).]

The injection of the same dose (0·1 mg. kg.) of diisopropyl fluorophosphate (DFP) into the right common carotid artery of rabbits resulted in 3 different behavioral states. The animals usually circled to the left, some however, turned to the right, and a few retained their normal behavior. Forced circling whether to the right or left is associated with an asymmetric reduction of acetylcholinesterase activity on the 2 sides of the brain. In animals that circle to the left, the right frontal cortex and right caudate nucleus were primarily involved, while in animals which turn to the right the frontal cortex on both sides of the brain as well as the right caudate nucleus are implicated. The fall of acetylcholinesterase from 90 to 54 per cent. of normal in the left frontal cortex was associated with a change in behavior, namely a reversal in direction of circling from the left to right.

E. D. W. (Chem. Abstr.)

*Cholinesterase Activity and Electroencephalograms During Circling Induced by the Intracarotid Injection of Diisopropyl Fluorophosphate (DFP). Harwood, C. Theresa.* [*Am. J. Physiol.*, **177**, 171 (1954).]

The cholinesterase content prior to and subsequent to (DFP) injections was determined in the cerebral cortex, caudate nucleus, thalamus, midbrain, cerebellum, and medulla of the rabbit brain. Electric potentials were recorded from the motor and limbic cortical areas, caudate nuclei, and thalami. The caudate nucleus shows the greatest depletion of enzyme following the administration of (DFP). However, the potentials recorded from the subcortical structures do not exhibit changes that can explain the adversive syndrome observed in rabbits following the intracarotid administration of (DFP). The ratio of mecholyl to acetylcholine hydrolyzing power of the enzyme is consistent. Since mecholyl and acetylcholine are diagnostic substrates for the identification of the true or type-E Enzyme, the data show that only the true enzyme is utilized in the hydrolysis of these substrates.

E. D. W. (Chem. Abstr.)

*Cerebral Arteriography in Chronic Carbon Disulfide Poisoning. Cesaro, Angelo Nunziante and Luccarelli, Saverio.* [*Folia Med. (Naples)*, **37**, 264 (1954).]

Various changes in the arterial pattern and appearance are described. The circulation is slowed down. Carbon disulfide poisoning causes essentially a syndrome of cerebral arteriosclerosis.

A. E. MEYER (Chem. Abstr.)

*Phosphoproteins and the Processes of Metabolism in the Brain. Lisovskaya, N. P.* [*Doklady Akad. Nauk. S.S.S.R.*, **95**, 1033 (1954).]

Experiments with rats with the aid of $P_{32}$ showed the following: (1) Phosphoproteins (I) are a real fraction of proteins in the rat brain which are characterized by specific metabolism. (2) The rate of their transformation greatly exceeds that of other P compounds, including nucleic acids. Their metabolism depends on oxidative processes in the cells and all blocking agents (NaCN, narcotics) hinder the (I) metabolism. The metabolism is connected with oxidative phosphorylation; in the presence of dinitrophenol the (I) metabolism declines. Although glucose can serve as the substrate whose oxidation is tied in with (I) metabolism, glutamic acid cannot so serve.

G. M. K. (Chem. Abstr.)

*Respiration and Hexokinase Activity on Rat-brain Homogenates in the Presence of Substances of Probable Keto Steroid Nature Extracted from Nervous Tissue. Marmori, M., et al.* [*Enzymologia*, **16**, 117 (1953).]

Neuroketone, a lipide solution extract from nervous tissue, inhibits the respiration and hexokinase activity of rat-brain homogenates.

ERICH HIRSCHBERG (Chem. Abstr.)

*Arterial Hypertension Provoked by Excitation of the Cerebral Cortex. Cicardo, V. H.* [*Rev. soc. argentina biol.*, **29**, 242 (1953).]

Monopolar electric stimulation of the cerebral cortex by means of a thin electrode passed through a trepanation of the skull of curarized, nonanesthetized dogs produced marked arterial hypertension when applied to motor and premotor areas. This is attributed to stimulation of the sympathico-adrenal system with resulting liberation of adrenaline from the adrenal medulla and noradrenaline from the sympathetic nerve endings. Barbiturates prevent completely the rise in blood pressure, sympathicolytics (hydergin, priscol) partially or totally prevent it, and hydantoinates diminish but do not abolish it.

L. E. GILSON (Chem. Abstr.)

*Neuraminic Acid in Cerebral Tissue of the White Rat. Chatagnon, C., and Chatagnon, P.* [*Compt. rend. soc. biol.*, **147**, 1992 (1953).]

Neuraminic acid is present in rat cerebral tissue in approximately the same proportion as in human and ox brains. It is also present in the mucin of the salivary glands and in the mucoprotein of the rat urine.

L. E. GILSON (Chem. Abstr.)

*Aldolases of the Brain. Palladin, A. V., and Polyakova, N. M.* [*Ukrain. Biokhim. Zhur.*, **21**, 341 (1949).]

Enzymic preparations obtained from the brains of animals such as gophers, rats, rabbits, dogs, and horned animals have high aldolase activity. A higher activity was found for dog and horned-animal cerebellum and gray matter of the cerebral lobes than for white matter and medulla. Aldolase activity for the rabbit in earlier developmental stages was less than for mature animals. Brain homogenate (1:100) and a substrate of the Na salt of fructose-1,6-diphosphate (1) were used. The Brain homogenate (1·2 ml. containing 12 mg. tissue) was added to a reaction mixture composed of 3 ml. acetate buffer of pH 6·7, 0·5 ml. of the Na salt of (1), 0·5 ml. of 2 per cent. $NaHSO_3$, and 0·8 ml. of water, a total volume of 6 ml. The samples were incubated at 37° for 1 hour, and 2 ml. of 10 per cent. $CCl_3COOH$ was then added, the control being a sample immediately fixed with $CCl_3COOH$. After preparation of the proteins, inorganic P and alkali-labile P were determined after 20 minutes hydrolysis at room temperature with 1N KOH. Inorganic P was determined according to the Fiske-SubbaRow method, and fructose according to Roe. Protein was determined by $H_2SO_4$ digestion of the homogenate followed by colorimetric Winkler determination.

CLAYTON F. HOLOWAY (Chem. Abstr.)

*Effects of Corticotropin and Various Convulsion-inducing Agents on the $P^{32}$ Content of Brain Phospholipides, Nucleoproteins, and Total Acid-soluble Phosphorus Compounds. Torda, Clara.* [*Am. J. Physiol.*, **177**, 179 (1954).]

Adrenocorticotropic hormone (ACTH) given in a single intraperitoneal injection (3 mg./100 g. body wt.) increased the $P^{32}$ content of the phospholipide fraction approximately by 31 per cent. in less than 15 minutes without significantly modifying the $P^{32}$ contents of the other P-containing fractions. Convulsions induced by electroshock (1-minute duration) and pentylenetetrazole (5-minute duration) resulted in a decrease of the concentration of the radioactivity of brain phospholipides without a significant change in the $P^{32}$ content of the other P-containing fractions. The results indicate that brain phospholipides are utilized during cerebral activity. During increased cerebral activity, including convulsions, a rapid breakdown of 1 of the constituents (probably a lecithin) of the brain phospholipides occurs. ACTH increases phospholipide synthesis.

E. D. WALTER (Chem. Abstr.)

*Relation of Glutamic Acid Metabolism to Certain Members of the Krebs Cycle in Brain. Bessmann, Samuel P.* [*Congr. intern. biochim., Résumés communs., 2^e^ Congr., Paris,* 1952, 31.]

The transamination of γ-aminobutyric acid is discussed. The further metabolism of succinic semialdehyde is still undetermined. In addition concentrations (0·01 M) of glutamic acid normally found in the brain stimulate the oxidation of malate, fumarate, and succinate by brain homogenates. The reaction is a transamination between glutamate and oxalacetate.

W. C. TOBIE (Chem. Abstr.)

*Labeling of Brain Phospholipides with Radioactive Phosphorus.* *Dawson, R. M. C.* [*Biochem. J.*, **57**, 237 (1954).]

In guinea-pig brain dispersions actively incorporating $P^{32}$ no appreciable incorporation was found in phosphatidylethanolamine, phosphatidylserine, or sphingomyelin, and the renewal of P in lecithin was also very slow. On the contrary, in actively respiring brain dispersions the renewal of diphosphoinositide P proceeds at an appreciable rate. But most of the incorporation of $P^{32}$ into the lipides of a brain dispersion occurs in association with the synthesis of a material solution in fat solvents, probably acidic in nature and containing glycerophosphate as part of its molecule. This distribution of radioactivity between the labeled phospholipides of brain is remarkably similar to that found in liver slices.

S. Morgulis (Chem. Abstr.)

*Acetylcholine as a Transmitter Substance in Sympathetic Ganglia.* *Kewitz, H.* [*Naunyn Schmiedebergs Arch. exptl. Pathol. Pharmakol.*, **222**, 323 (1954).]

From experiments with the perfused superior cervical ganglion of the cat, it is concluded that scopolamine, atropine, and trasentine H inhibit the nicotine-like action of acetylcholine in sympathetic ganglia as well as in the post-ganglionic end points of parasympathetic fibers. The transmitter action of the ganglia, however, is not impaired. This proves that acetylcholine is not necessary for the transmitter function. Procaine acts fundamentally like the parasympatholytic substances. Surface anesthetics such as pantocaine and procaineamide inhibit preferentially the transmitter action and slightly the acetylcholine excitation. Phenothiazine derivatives as phenergan, latibon, and megaphene have both inhibiting qualities. The inhibition of acetylcholine is stronger and lasts longer than the disturbance of transmission.

A. E. Meyer (Chem. Abstr.)

*Differentiation Between Excitation by Acetylcholine and the Function of Transmission of Sympathetic Ganglia by Means of Perfusion Fluids of Varied Composition.* *Kewitz, Helmut and Reinert, Harald.* [*Naunyn-Schmiedebergs Arch. exptl. Pathol. Pharmakol.*, **222**, 315 (1954).]

Lack of glucose or K in the perfusion fluid of isolated superior cervical ganglia of the cat causes a decrease in the sensitivity to acetylcholine (1). This does not interfere with the transmission of preganglionic electric impulses. With reference to excitation by (1) the perfusion fluid may contain meso-inositol in place of glucose. Phytin inhibits the (1) action completely and faster than lack of glucose. Ca ions produce strong spontaneous excitation; when this subsides the function of transmission is paralyzed and the (1) effect is reinforced and prolonged. Lack of Na causes abolition of both functions within a short time.

A. E. Meyer (Chem. Abstr.)

*Potassium Content of cerebrospinal Fluid.* *Lowenthal, A.* [*Compt. rend. soc. biol.*, **147**, 2059 (1953).]

Average values found were 12·2 mg. per cent. for normal men, 12·7 mg. per cent. for women, and somewhat lower values for young children.

L. E. Gilson (Chem. Abstr.)

## 2. Pharmacology and Treatment

*The Effect of Carbon Dioxide on Cerebral Blood Flow, Spinal Fluid Pressure, and Brain Volume During Pentothal Sodium Anesthesia.* *Wilson, W. P., et al.* [*Current Researches Anesthesia and Analgesia*, **32**, 268 (1953).]

In 10 patients light thiopental anesthesia produced no significant decrease in cerebral blood flow but lowered cerebral metabolism and arterial-venous O difference. Inhalation of 7 per cent. $CO_2$ for 4–8 minutes increased cerebrospinal fluid pressure, cerebral blood flow, and brain volume.

Karl F. Urbach (Chem. Abstr.)

*Re-evaluation of Metrazol in Experimental Barbiturate Poisoning.* *Bailey, Herbert A., et al.* [*Current Researches Anesthesia and Analgesia*, **32**, 274 (1953).]

In experimental barbiturate poisoning of 17 dogs with pentobarbital, metrazol therapy under varying conditions appeared to contribute little to the survival of the animals and was found capable of severe blood pressure depression without increasing neuro-muscular excitability.

Karl F. Urbach (Chem. Abstr.)

*The Evaluation of Pentylenetetrazole as a Barbiturate Antagonist.* *Fazekas, Joseph F., and Koppanyi, Theodore.* [*Current Researches Anesthesia and Analgesia*, 33, 58 (1954).]

The antagonistic activity of pentylenetetrazole against pentobarbital is demonstrated in mice receiving $L.D._{98}$ and higher doses of the barbiturate. The interpretation of their experimental data by Bailey *et al.* is criticized.

Karl F. Urbach (Chem. Abstr.)

*The Distribution of Mescaline (Labeled with Radioactive Carbon*$^{14}$*) in the Animal Organism and its Association with the Proteins of the Liver. Block, Wolfram and Block, Katharine* [*Congr. intern. biochim., Résumés communs., 2^e^ Congr., Paris*, 1952, 429.]

Mice more closely resemble men in the rate of excretion of mescaline (1) in the urine than do other animals. In white mice to which (1) (labeled with $C^{14}$) was administered, the brain was always the least radioactive of the organs. The (1) was rather rapidly incorporated in the proteins of the liver. After separation from the proteins, (1) could be identified by chromatography and electrophoresis on paper, followed by conversion to the picrate.

W. C. Tobie (Chem. Abstr.)

*Depression by Barbiturates of the Metabolism of Electrically Stimulated Cerebral Tissues. McIlwain, H.* [*Congr. intern. biochim., Résumés communs.*, $2^e$ *Congr., Paris*, 1952, 440.]

Modifications of cerebral activity by barbiturates *in vivo* are discussed. It has been found possible to stimulate the metabolism of isolated cerebral tissues by electric methods (not described). Phenobarbital, butethal, and dial inhibit respiration of electrically stimulated sections of rat or guinea-pig cerebral cortex at concentrations (not stated) which have little or no effect on respiration in the absence of electric stimulation. These compounds also decreased the lactic acid which accumulated (with glucose as substrate) in reaction mixtures with stimulated tissue. This change occurs during narcosis *in vivo* and is the opposite of that induced by the drugs in unstimulated tissue *in vitro*. Chloral (and to some extent high concentrations of Mg. ions) had a similar action. Inhibition of stimulated tissue was promptly reversed on removing the drug.

W. C. Tobie (Chem. Abstr.)

*Treatment of Parkinsonism and Other Disturbances of the Extrapyramidal Motor System. Luyendijk, L.* [*Vorderingen Geneesk.*, 1945–48, 354 (1949); *Excerpta Med., Sect. VIII*, **3**, 366 (1950).]

A discussion and review, including the pharmacological action of different compounds.

W. C. Tobie (Chem. Abstr.)

*Cholinesterase Activity of the Nervous Tissue in Acute and Chronic Intoxication from Bulbocapnine. Pappalardo, Piero.* [*Acta Neurol. (Naples)*, **7**, 208 (1952).]

In rats intramuscularly injected with 30 mg. bulbocapnine/kg. the cholinesterase activity in the cerebellum (especially by repeated daily treatments), in the nuclei of the brain basis, in the encephalic trunk, and in the bone marrow was lower, but in the brain cortex and bulb (especially by repeated treatments in the same day) higher than in controls.

C. Scandura (Chem. Abstr.)

*The Use of Correctives in the Prevention of Barbiturate Intoxication. Koppanyi, Theodore and Fazekas, Joseph F.* [*Am. J. Med. Sci.*, **226**, 597 (1953).]

Pentylenetetrazole is clinically and pharmaceutically the most suitable analeptic to use in barbiturate preparations for preventing poisoning upon overdosage. A critical ratio has been established for combining pentylenetetrazole with phenobarbital Na at 3:2, and pentylenetetrazole with pentobarbital or secobarbital Na at 3:1.

Marion Horn Peskin (Chem. Abstr.)

*The Actions of Barbiturates on the Contractions of Voluntary Muscle. Kraatz, Charles P., and Gluckman, Melvyn I.* [*J. Pharmacol., Exptl. Therap.*, **111**, 120 (1954).]

Four types of effects on voluntary muscle function are evoked by relatively low concentrations of the barbiturates, the incidence and intensity of the effect varying with the barbiturates and with the test object (dog, rabbit, and frog preparations). The 4 types are: (*a*) Potentiation of the maximum twitch by a probable direct action on the fiber. The thiobarbiturates are more active in this respect and the relative potency of the compounds parallels their pharmacological potency generally and their protein-binding affinity. (*b*) A curare-like activity which augments the action of curare on artificially stimulated fast muscle. The oxybarbiturates regularly manifest this property; the thiobarbiturates do so only under special conditions. (*c*) A type of mild anticurare activity, characteristic only of the thiobarbiturates. (*d*) A protective action against curare demonstrable on naturally activited muscles of the neck and chest and limited to just a few of the compounds. Barbiturates in general appear able to penetrate muscle.

L. E. Gilson (Chem. Abstr.)

*Histochemical Studies on the Brain Glycogen of Rabbits and its Changes During Insulin Hypoglycemia. Shimizu, Nobuo and Inoue, Gyozaburo.* [*Med. J. Osaka Univ.*, **3**, 337–43 (1952).]

Histochemical examination of tissues from rabbits with insulin hypoglycemia showed severe loss of glycogen (1) in the cerebral cortex and striatum. A lesser change was noted in the cerebellum. The neocortex had nearly complete loss of (1) from the 6 layers. The hippocampus is deprived of (1), while the dentate gyrus is affected only slightly. The nerve cells containing (1) are only slightly affected by hypoglycemia.

M. J. Carver (Chem. Abstr.)

*Influence of Narcosis Upon the Formation of Phosphopyruvic Acid in the Brain. Ivanenko E. Kh.* [*Ukrain. Biokhim. Zhur.*, **21,** 350 (1949).]

Phosphopyruvic acid (1) was not found in the normal tissues of white mice, rats, or rabbits. An average of 24·6 mg. per cent. of phosphopyruvic acid P appeared in white-mouse brain under the influence of ether narcosis. The inorganic p decreased from 76·3 mg. per cent. to 58·4 or a 23·5 per cent. decrease with respect to the norm, in narcosis. Standard tests for (1) synthesis from lactate added to the brain tissue indicated: (*a*) that the tissue of rabbit and white-mouse brain, to which phosphate and lactate have been added, do not contain (1) in the absence of narcosis, (*b*) that (1)–P in the brain under the same conditions, with narcosis, is found in the amount of 14·–52 mg. per cent., (*c*) that general narcosis intensifies the (1) synthesis process from added lactate.

Clayton F. Holoway (Chem. Abstr.)

*Lysergic Acid Ethylamide (LAE), a New, Strong, Sedative, Psychotic Agent from Ergot. Solms, H.* [*Schweiz. med. Wochschr.*, **83,** 356 (1953).]

The action of lysergic acid ethylamide (1) was studied on both healthy and mentally ill patients. From 0·5 to 0·75 mg. of (1) subcutaneously produces in the healthy human a schizophrenic-like condition of adynamia, indifference, and lack of will power with intensive depersonalization phenomena without sleep. Electroencephalograms show that the adynamia from (1) is completely different from barbiturate or physiological sleep.

Harold S. Bailey (Chem. Abstr.)

*A Biochemical and Pharmacological Suggestion About Certain Mental Disorders. Woolley, D. W., and Shaw, E.* [*Proc. Natl. Acad. Sci. U.S.*, **40,** 228 (1954).]

A general discussion of the hypothesis that serotonin may play a role in mental processes and that the suppression of its action may result in a mental disorder.

J. D. Taylor (Chem. Abstr.)

*Method for the Determination of the Effects of Drugs on the Pain Threshold of Human Subjects. Deneau, G. A., et al.* [*Can. J. Med. Sci.*, **31,** 387 (1953).]

The method consists of inducing a sharp pain in the calf muscles by applying pressure with a sphygmomanometer cuff; the pressure required to induce pain is taken as a measure of the pain threshold. The normal threshold can be determined with an accuracy of ±10 mm. Hg pressure. With placebos, a maximum increase of 4 per cent. over the normal pain threshold occurred one hour after administration. Acetylsalicylic acid produced an increase of approximately 20 per cent. at the same period; this was significantly greater than placebo effects. The effect of mild narcotic agents, given orally, upon the pain threshold was also measured. Codeine phosphate and pethidine-HCl both produced a significant increase in the pain threshold. The method permits the use of untrained human subjects and is sufficiently sensitive to measure the effects of the antipyretic nalgesics.

A. E. Teeri (Chem. Abstr.)

*Methylpentynol as a Hypnotic for Old People. Simpson, Ronald G.* [*Lancet*, **266,** 883 (1954).]

Methylparafynol (3-methylpentyne-3-ol) was an effective hypnotic without significant side effects in 61 of 94 patients 65 years and older.

Barbara R. Murray (Chem. Abstr.)

*Clinical Use of Reserpine in Geriatrics. Harris, Raymond.* [*Ann. N.Y. Acad. Sci.*, **59,** 95 (1954).]

In a "double blind" study, the administration of reserpine to 26 elderly hypertensive patients, with an average age of 68 years, lowered the systolic blood pressure 8 per cent. and the diastolic blood pressure 11 per cent. and decreased the average heart rate. The sedative and tranquilizing effects of reserpine appeared to be of value in reducing the emotional and mental tensions of geriatric patients.

E. W. Grant (Chem. Abstr.)

*Human Pharmacology of Reserpine. Winsor, Travis.* [*Ann. N.Y. Acad. Sci.*, **59,** 61 (1954).]

Reserpine (I) was administered to 65 patients representing various types of hypertension. Results indicated that (I) was a good hypotensive agent, being most effective in middle-aged patients with hypertension of a few years' duration, with severe diastolic elevations in their blood pressure and with moderate amounts of organic damage to organs. The action of (I) was increased by combining it with hydrazinophthalazine (II). In certain individuals, the addition of azamethonium to (I) and (II) was more effective than the combination of (I) and (II).

E. W. Grant (Chem. Abstr.)

*Clinical Usage of Rauwolfia Alkaloids, including Reserpine. Wilkins, Robert W.* [*Ann. N.Y. Acad. Sci.*, **59**, 36 (1954).]

The most beneficial effects of Rauwolfia (I) and reserpine (II) are the decrease of neurotic symptoms in all patients and the lowering of blood pressure, particularly in the young, labile, neurotic hypertensives with tachycardia. (I) and (II) have a striking additive, if not synergistic, effect when given in combination with other hypotensive agents. Both (I) and (II) cause sedation, bradycardia, hypotension, nasal stuffiness, and weight gain. They can be taken apparently indefinitely and do not result in tolerance or addiction.

E. W. Grant (Chem. Abstr.)

*Pharmacology of Rauwolfia Alkaloids, including Reserpine. Plummer, Albert, J., et al.* [*Ann. N.Y. Acad. Sci.*, **59**, 8 (1954).]

Reserpine possesses both the central nervous depressant and hypotensive actions of the root of *R. serpentina.* Its effects, including sedation, reduced emotional response, peripheral autonomic alterations, and circulatory changes, are caused by an alteration of sympathetic-parasympathetic balance by partial supression of sympathetic predominance at the hypothalamic level.

E. W. Grant (Chem. Abstr.)